

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 15/86, 15/35, 5/10, A61K 48/00	A2	(11) International Publication Number: WO 00/28061 (43) International Publication Date: 18 May 2000 (18.05.00)
(21) International Application Number: PCT/US99/25694 (22) International Filing Date: 2 November 1999 (02.11.99) (30) Priority Data: 60/107,114 5 November 1998 (05.11.98) US (71) Applicant (for all designated States except US): THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA [US/US]; Suite 300, 3700 Market Street, Philadelphia, PA 19104-3147 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): WILSON, James, M. [US/US]; 1350 N. Avignon Drive, Gladwyne, PA 19035 (US). XIAO, Weidong [CN/US]; Apartment P4, 155 Washington Lane, Jenkintown, PA 19046 (US). (74) Agents: KODROFF, Cathy, A. et al.; Howson & Howson, Spring House Corporate Center, P.O. Box 457, Spring House, PA 19477 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: ADENO-ASSOCIATED VIRUS SEROTYPE 1 NUCLEIC ACID SEQUENCES, VECTORS AND HOST CELLS CONTAINING SAME (57) Abstract The nucleic acid sequences of adeno-associated virus (AAV) serotype 1 are provided, as are vectors and host cells containing these sequences and functional fragments thereof. Also provided are methods of delivering genes via AAV-1 derived vectors.		

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

ADENO-ASSOCIATED VIRUS SEROTYPE I NUCLEIC ACID SEQUENCES, VECTORS AND HOST CELLS CONTAINING SAME

This work was supported by the National Institutes of Health, grant no. P30
DK47757-06 and PO1 HD32649-04. The US government may have certain rights in
5 this invention.

Field of the Invention

This invention relates generally to viral vector, and more particularly, to
recombinant viral vectors useful for gene delivery.

Background of the Invention

10 Adeno-associated viruses are small, single-stranded DNA viruses which
require helper virus to facilitate efficient replication [K.I. Berns, *Parvoviridae: the
viruses and their replication*, p. 1007-1041, in F.N. Fields et al., Fundamental
virology, 3rd ed., vol. 2, (Lippencott-Raven Publishers, Philadelphia, PA) (1995)].
The 4.7 kb genome of AAV is characterized by two inverted terminal repeats (ITR)
15 and two open reading frames which encode the Rep proteins and Cap proteins,
respectively. The Rep reading frame encodes four proteins of molecular weight 78
kD, 68 kD, 52 kD and 40 kD. These proteins function mainly in regulating AAV
replication and integration of the AAV into a host cell's chromosomes. The Cap
reading frame encodes three structural proteins in molecular weight 85 kD (VP 1), 72
20 kD (VP2) and 61 kD (VP3) [Berns, cited above]. More than 80% of total proteins in
AAV virion comprise VP3. The two ITRs are the only cis elements essential for AAV
replication, packaging and integration. There are two conformations of AAV ITRs
called "flip" and "flop". These differences in conformation originated from the
replication model of adeno-associated virus which use the ITR to initiate and reinitiate
25 the replication [R.O. Snyder et al., J. Virol., 67:6096-6104 (1993); K.I. Berns,
Microbiological Reviews, 54:316-329 (1990)].

AAVs have been found in many animal species, including primates, canine,
fowl and human [F.A. Murphy et al., "The Classification and Nomenclature of
Viruses: Sixth Report of the International Committee on Taxonomy of Viruses",

Archives of Virology, (Springer-Verlag, Vienna) (1995)]. In addition to five known primate AAVs (AAV-1 to AAV-5), AAV-6, another serotype closely related to AAV-2 and AAV-1 has also been isolated [E. A. Rutledge et al., J. Virol., 72:309-319 (1998)]. Among all known AAV serotypes, AAV-2 is perhaps the most well-
5 characterized serotype, because its infectious clone was the first made [R.J. Samulski et al., Proc. Natl. Acad. Sci. USA, 79:2077-2081 (1982)]. Subsequently, the full sequences for AAV-3A, AAV-3B, AAV-4 and AAV-6 have also been determined [Rutledge, cited above; J.A.Chiorini et al., J. Virol., 71:6823-6833 (1997); S. Muramatsu et al., Virol., 221:208-217 (1996)]. Generally, all AAVs share more than
10 80% homology in nucleotide sequence.

A number of unique properties make AAV a promising vector for human gene therapy [Muzyczka, Current Topics in Microbiology and Immunology, 158:97-129 (1992)]. Unlike other viral vectors, AAVs have not been shown to be associated with any known human disease and are generally not considered pathogenic. Wild type
15 AAV is capable of integrating into host chromosomes in a site specific manner [R. M. Kotin et al., Proc. Natl. Acad. Sci. USA, 87:2211-2215 (1990)- R.J. Samulski, EMBO J., 10(12):3941-3950 (1991)]. Recombinant AAV vectors can integrate into tissue cultured cells in chromosome 19 if the rep proteins are supplied in *trans* [C. Balague et al., J. Virol., 71:3299-3306 (1997); R. T. Surosky et al., J. Virol.,
20 71:7951-7959 (1997)]. The integrated genomes of AAV have been shown to allow long term gene expression in a number of tissues, including, muscle, liver, and brain [K. J. Fisher, Nature Med., 3(3):306-312 (1997); R. O. Snyder et al., Nature Genetics, 16:270-276 (1997); X. Xiao et al., Experimental Neurology, 144:113-124 (1997); Xiao, J. Virol., 70(11):8098-8108 (1996)].

25 AAV-2 has been shown to be present in about 80-90% of the human population. Earlier studies showed that neutralizing antibodies for AAV-2 are prevalent [W. P. Parks et al., J. Virol., 2:716-722 (1970)]. The presence of such antibodies may significantly decrease the usefulness of AAV vectors based on AAV-2 despite its other merits. What are needed in the art are vectors characterized by the

advantages of AAV-2, including those described above, without the disadvantages, including the presence of neutralizing antibodies.

Summary of the Invention

In one aspect, the invention provides an isolated AAV-1 nucleic acid molecule
5 which is selected from among SEQ ID NO: 1, the strand complementary to SEQ ID NO: 1, and cDNA and RNA sequences complementary to SEQ ID NO: 1 and its complementary strand.

In another aspect, the present invention provides AAV ITR sequences, which include the 5' ITR sequences, nt 1 to 143 of SEQ ID NO: 1; the 3' ITR sequences, nt
10 4576 to 4718 of SEQ ID NO: 1, and fragments thereof.

In yet another aspect, the present invention provides a recombinant vector comprising an AAV-1 ITR and a selected transgene. Preferably, the vector comprises both the 5' and 3' AAV-1 ITRs between which the selected transgene is located.

In still another aspect, the invention provides a recombinant vector comprising
15 an AAV-1 P5 promoter having the sequence of nt 236 to 299 of SEQ ID NO: 1 or a functional fragment thereof.

In a further aspect, the present invention provides a nucleic acid molecule encoding an AAV-1 rep coding region and an AAV-1 cap coding region.

In still another aspect, the present invention provides a host cell transduced with a
20 recombinant viral vector of the invention. The invention further provides a host cell stably transduced with an AAV-1 P5 promoter of the invention.

In still a further aspect, the present invention provides a pharmaceutical composition comprising a carrier and a vector of the invention.

In yet another aspect, the present invention provides a method for AAV--
25 mediated delivery of a transgene to a host involving the step of delivering to a selected host a recombinant viral vector comprising a selected transgene under the control of sequences which direct expression thereof and an adeno-associated virus 1 (AAV-1) virion.

In another aspect, the invention provides a method for in vitro production of a selected gene product using a vector of the invention.

Other aspects and advantages of the invention will be readily apparent to one of skill in the art from the detailed description of the invention.

5 Brief Description of the Drawings

Figs. 1A-1C illustrate the alignment of nucleotides of AAV-1 [SEQ ID NO: 1], AAV-2 [SEQ ID NO: 18] and AAV-6 [SEQ ID NO: 19]. The alignment was done with MacVector 6.0. The full sequences of AAV-1 are shown in the top line. Nucleotides in AAV-2 and AAV-6 identical to AAV-1 are symbolized by "." and gaps by "-". Some of the conserved features among AAVs are marked in this figure. Note the 3' ITRs of AAV-1 and AAV-6 are shown in different orientations.

Fig. 2 illustrates the predicted secondary structure of AAV-1 ITR. The nucleotides in AAV-2 and AAV-6 are shown in italic and bold respectively.

Fig. 3A illustrates a hypothesis of how AAV-6 arose from the homologous recombination between AAV-1 and AAV-2. The major elements of AAV-1 are indicated in the graph. A region that is shared between AAV-1, AAV-2 and AAV-6 is shown in box with waved lines.

Fig. 3B is a detailed illustration of a 71 bp homologous region among AAV-1, AAV-2 and AAV-6. Nucleotides that differ among these serotypes are indicated by arrows.

Fig. 4A is a bar chart illustrating expression levels of human alpha 1 anti-trypsin (α 1AT) in serum following delivery of hAAT via recombinant AAV-1 and recombinant AAV-2 viruses.

Fig. 4B is a bar chart illustrating expression levels of erythropoietin (epo) in serum following delivery of the epo gene via recombinant AAV-1 and recombinant AAV-2 viruses.

Fig. 5A is a bar chart illustrating expression levels of α 1AT in liver following delivery of α 1AT as described in Example 7.

Fig. 5B is a bar chart demonstrating expression levels of epo in liver following delivery of epo as described in Example 7.

Fig. 5C is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-1 following delivery of α 1AT or epo to liver as described in Example 7.

5 Fig. 5D is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-2 following delivery of α 1AT or epo to liver as described in Example 7.

Fig. 6A is a bar chart illustrating expression levels of α 1AT in muscle following delivery of α 1AT as described in Example 7.

Fig. 6B is a bar chart demonstrating expression levels of epo in muscle
10 following delivery of epo as described in Example 7.

Fig. 6C is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-1 following delivery of α 1AT or epo to muscle as described in Example 7.

Fig. 6D is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-2 following delivery of α 1AT or epo to muscle as described in Example 7.

15 Detailed Description of the Invention

The present invention provides novel nucleic acid sequences for an adeno-- associated virus of serotype 1 (AAV-1). Also provided are fragments of these AAV-1 sequences. Among particularly desirable AAV-1 fragments are the inverted terminal repeat sequences (ITRs), rep and cap. Each of these fragments may be readily
20 utilized, e.g., as a cassette, in a variety of vector systems and host cells. Such fragments may be used alone, in combination with other AAV-1 sequences or fragments, or in combination with elements from other AAV or non-AAV viral sequences. In one particularly desirable embodiment, a cassette may contain the AAV-1 ITRs of the invention flanking a selected transgene. In another desirable
25 embodiment, a cassette may contain the AAV-1 rep and/or cap proteins, e.g., for use in producing recombinant (rAAV) virus.

Thus, the AAV-1 sequences and fragments thereof are useful in production of rAAV, and are also useful as antisense delivery vectors, gene therapy vectors, or vaccine vectors. The invention further provides nucleic acid molecules, gene delivery

vectors, and host cells which contain the AAV-1 sequences of the invention. Also provided a novel methods of gene delivery using AAV vectors.

As described herein, the vectors of the invention containing the AAV-1 capsid proteins of the invention are particularly well suited for use in applications in which the neutralizing antibodies diminish the effectiveness of other AAV serotype based vectors, as well as other viral vectors. The rAAV vectors of the invention are particularly advantageous in rAAV readministration and repeat gene therapy.

These and other embodiments and advantages of the invention are described in more detail below. As used throughout this specification and the claims, the term “comprising” is inclusive of other components, elements, integers, steps and the like.

I. AAV-1 NUCLEIC ACID AND PROTEIN SEQUENCES

The AAV-1 nucleic acid sequences of the invention include the DNA sequences of SEQ ID NO: 1 (Figs. 1A-1C), which consists of 4718 nucleotides. The AAV-1 nucleic acid sequences of the invention further encompass the strand which is complementary to SEQ ID NO: 1, as well as the RNA and cDNA sequences corresponding to SEQ ID NO: 1 and its complementary strand. Also included in the nucleic acid sequences of the invention are natural variants and engineered modifications of SEQ ID NO: 1 and its complementary strand. Such modifications include, for example, labels which are known in the art, methylation, and substitution of one or more of the naturally occurring nucleotides with an analog.

Further included in this invention are nucleic acid sequences which are greater than 85%, preferably at least about 90%, more preferably at least about 95%, and most preferably at least about 98 - 99% identical or homologous to SEQ ID NO:1. The term “percent sequence identity” or “identical” in the context of nucleic acid sequences refers to the residues in the two sequences which are the same when aligned for maximum correspondence. The length of sequence identity comparison may be over the full-length sequence, or a fragment at least about nine nucleotides, usually at least about 20 - 24 nucleotides, at least about 28 - 32 nucleotides, and preferably at least about 36 or more nucleotides. There are a number of different

algorithms known in the art which can be used to measure nucleotide sequence identity. For instance, polynucleotide sequences can be compared using Fasta, a program in GCG Version 6.1. Fasta provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences
5 (Pearson, 1990, herein incorporated by reference). For instance, percent sequence identity between nucleic acid sequences can be determined using Fasta with its default parameters (a word size of 6 and the NOPAM factor for the scoring matrix) as provided in GCG Version 6.1, herein incorporated by reference.

The term "substantial homology" or "substantial similarity," when referring to
10 a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 95 - 99% of the sequence.

Also included within the invention are fragments of SEQ ID NO: 1, its
15 complementary strand, cDNA and RNA complementary thereto. Suitable fragments are at least 15 nucleotides in length, and encompass functional fragments which are of biological interest. Certain of these fragments may be identified by reference to Figs. 1A-1C. Examples of particularly desirable functional fragments include the AAV-1 inverted terminal repeat (ITR) sequences of the invention. In contrast to the 145 nt
20 ITRs of AAV-2, AAV-3, and AAV-4, the AAV-1 ITRs have been found to consist of only 143 nucleotides, yet advantageously are characterized by the T-shaped hairpin structure which is believed to be responsible for the ability of the AAV-2 ITRs to direct site-specific integration. In addition, AAV-1 is unique among other AAV serotypes, in that the 5' and 3' ITRs are identical. The full-length 5' ITR sequences of
25 AAV-1 are provided at nucleotides 1-143 of SEQ ID NO: 1 (Fig. 1A) and the full-length 3' ITR sequences of AAV-1 are provided at nt 4576-4718 of SEQ ID NO: 1 (Fig. 1C). One of skill in the art can readily utilize less than the full-length 5' and/or 3' ITR sequences for various purposes and may construct modified ITRs using conventional techniques, e.g., as described for AAV-2 ITRs in Samulski et al, Cell,
30 33:135-143 (1983).

Another desirable functional fragment of the AAV-1 genome is the P5 promoter of AAV-1 which has sequences unique among AAV P5 promoters, while maintaining critical regulatory elements and functions. This promoter is located within nt 236 - 299 of SEQ ID NO: 1 (Fig. 1A). Other examples of functional fragments of interest include the sequences at the junction of the rep/cap, e.g., the sequences spanning nt 2306-2223, as well as larger fragments which encompass this junction which may comprise 50 nucleotides on either side of this junction. Still other examples of functional fragments include the sequences encoding the rep proteins. Rep 78 is located in the region of nt 334 - 2306 of SEQ ID NO: 1; Rep 68 is located in the region of nt 334-2272, and contains an intron spanning nt 1924-2220 of SEQ ID NO: 1. Rep 52 is located in the region of nt 1007 - 2304 of SEQ ID NO: 1; rep 40 is located in the region of nt 1007 - 2272, and contains an intron spanning nt 1924-2246 of SEQ ID NO: 1. Also of interest are the sequences encoding the capsid proteins, VP 1 [nt 2223-4431 of SEQ ID NO: 1], VP2 [nt 2634-4432 of SEQ ID NO: 1] and VP3 [nt 2829-4432 of SEQ ID NO: 1]. Other fragments of interest may include the AAV-1 P19 sequences, AAV-1 P40 sequences, the rep binding site, and the terminal resolute site (TRS).

The invention further provides the proteins and fragments thereof which are encoded by the AAV-1 nucleic acids of the invention. Particularly desirable proteins include the rep and cap proteins, which are encoded by the nucleotide sequences identified above. These proteins include rep 78 [SEQ ID NO:5], rep 68 [SEQ ID NO:7], rep 52 [SEQ ID NO:9], rep 40 [SEQ ID NO: 11], vpl [SEQ ID NO: 13], vp2 [SEQ ID NO: 15], and vp3 [SEQ IID NO: 17] and functional fragments thereof while the sequences of the rep and cap proteins have been found to be closely related to those of AAV-6, there are differences in the amino acid sequences (see Table 1 below), as well as differences in the recognition of these proteins by the immune system. However, one of skill in the art may readily select other suitable proteins or protein fragments of biological interest. Suitably, such fragments are at least 8 amino acids in length. However, fragments of other desired lengths may be readily utilized.

Such fragments may be produced recombinantly or by other suitable means, e.g., chemical synthesis.

The sequences, proteins, and fragments of the invention may be produced by any suitable means, including recombinant production, chemical synthesis, or other synthetic means. Such production methods are within the knowledge of those of skill in the art and are not a limitation of the present invention.

II. VIRAL VECTORS

In another aspect, the present invention provides vectors which utilize the AAV-1 sequences of the invention, including fragments thereof, for delivery of a heterologous gene or other nucleic acid sequences to a target cell. Suitably, these heterologous sequences (i.e., a transgene) encode a protein or gene product which is capable of being expressed in the target cell. Such a transgene may be constructed in the form of a "minigene". Such a "minigene" includes selected heterologous gene sequences and the other regulatory elements necessary to transcribe the gene and express the gene product in a host cell. Thus, the gene sequences are operatively linked to regulatory components in a manner which permit their transcription. Such components include conventional regulatory elements necessary to drive expression of the transgene in a cell containing the viral vector. The minigene may also contain a selected promoter which is linked to the transgene and located, with other regulatory elements, within the selected viral sequences of the recombinant vector.

Selection of the promoter is a routine matter and is not a limitation of this invention. Useful promoters may be constitutive promoters or regulated (inducible) promoters, which will enable control of the timing and amount of the transgene to be expressed. For example, desirable promoters include the cytomegalovirus (CMV) immediate early promoter/enhancer [see, e.g., Boshart et al, Cell, 41:521-530 (1985)], the Rous sarcoma virus LTR promoter/enhancer, and the chicken cytoplasmic β -actin promoter [T. A. Kost et al, Nucl. Acids Res., 11(23):8287 (1983)]. Still other desirable promoters are the albumin promoter and an AAV P5 promoter. Optionally, the selected promoter is used in conjunction with a heterologous enhancer, e.g., the β -

actin promoter may be used in conjunction with the CMV enhancer. Yet other suitable or desirable promoters and enhancers may be selected by one of skill in the art.

The minigene may also desirably contain nucleic acid sequences heterologous to the viral vector sequences including sequences providing signals required for efficient polyadenylation of the transcript (poly-A or pA) and introns with functional splice donor and acceptor sites. A common poly-A sequence which is employed in the exemplary vectors of this invention is that derived from the papovavirus SV-40. The poly-A sequence generally is inserted in the minigene downstream of the transgene sequences and upstream of the viral vector sequences. A common intron sequence is also derived from SV-40, and is referred to as the SV40 T intron sequence. A minigene of the present invention may also contain such an intron, desirably located between the promoter/enhancer sequence and the transgene. Selection of these and other common vector elements are conventional [see, e.g., Sambrook et al, "Molecular Cloning. A Laboratory Manual", 2d edit., Cold Spring Harbor Laboratory, New York (1989) and references cited therein] and many such sequences are available from commercial and industrial sources as well as from Genebank.

The selection of the transgene is not a limitation of the present invention. Suitable transgenes may be readily selected from among desirable reporter genes, therapeutic genes, and optionally, genes encoding immunogenic polypeptides. Examples of suitable reporter genes include β -galactosidase (β -gal), an alkaline phosphatase gene, and green fluorescent protein (GFP). Examples of therapeutic genes include, cytokines, growth factors, hormones, and differentiation factors, among others. The transgene may be readily selected by one of skill in the art. See, e.g., WO 98/09657, which identifies other suitable transgenes.

Suitably, the vectors of the invention contain, at a minimum, cassettes which consist of fragments of the AAV-1 sequences and proteins. In one embodiment, a vector of the invention comprises a selected transgene, which is flanked by a 5' ITR and a 3' ITR, at least one of which is an AAV-1 ITR of the invention. Suitably,

vectors of the invention may contain a AAV-1 P5 promoter of the invention. In yet another embodiment, a plasmid or vector of the invention contains AAV-1 rep sequences. In still another embodiment, a plasmid or vector of the invention contains at least one of the AAV-1 cap proteins of the invention. Most suitably, these AAV-1-derived vectors are assembled into viral vectors, as described herein.

A. AAV Viral Vectors

In one aspect, the present invention provides a recombinant AAV-1 viral vector produced using the AAV-1 capsid proteins of the invention. The packaged rAAV-1 virions of the invention may contain, in addition to a selected minigene, other AAV-1 sequences, or may contain sequences from other AAV serotypes.

Methods of generating rAAV virions are well known and the selection of a suitable method is not a limitation on the present invention. See, e.g., K. Fisher et al, J. Virol., 70:520-532 (1993) and US Patent 5,478,745. In one suitable method, a selected host cell is provided with the AAV sequence encoding a rep protein, the gene encoding the AAV cap protein and with the sequences for packaging and subsequent delivery. Desirably, the method utilizes the sequences encoding the AAV-1 rep and/or cap proteins of the invention.

In one embodiment, the rep/cap genes and the sequences for delivery are supplied by co-transfection of vectors carrying these genes and sequences. In one currently preferred embodiment, a cis (vector) plasmid, a trans plasmid containing the rep and cap genes, and a plasmid containing the adenovirus helper genes are co-transfected into a suitable cell line, e.g., 293. Alternatively, one or more of these functions may be provided in trans via separate vectors, or may be found in a suitably engineered packaging cell line.

An exemplary cis plasmid will contain, in 5' to 3' order, AAV 5' ITR, the selected transgene, and AAV 3' ITR. In one desirable embodiment, at least one of the AAV ITRs is a 143 nt AAV-1 ITR. However, other AAV serotype ITRs may be readily selected. Suitably, the full-length ITRs are utilized. However, one of skill in

the art can readily prepare modified AAV ITRs using conventional techniques. Similarly, methods for construction of such plasmids is well known to those of skill in the art.

A trans plasmid for use in the production of the rAAV-1 virion particle
5 may be prepared according to known techniques. In one desired embodiment, this plasmid contains the rep and cap proteins of AAV-1, or functional fragments thereof. Alternatively, the rep sequences may be from another selected AAV serotype.

The cis and trans plasmid may then be co-transfected with a wild-type
10 helper virus (e.g., Ad2, Ad5, or a herpesvirus), or more desirably, a replication - defective adenovirus, into a selected host cell. Alternatively, the cis and trans plasmid may be co-transfected into a selected host cell together with a transfected plasmid which provides the necessary helper functions. Selection of a suitable host cell is well within the skill of those in the art and include such mammalian cells as 293 cells, HeLa cells, among others.

15 Alternatively, the cis plasmid and, optionally the trans plasmid, may be transfected into a packaging cell line which provides the remaining helper functions necessary for production of a rAAV containing the desired AAV-1 sequences of the invention. An example of a suitable packaging cell line, where an AAV-2 capsid is desired, is B-50, which stably expresses AAV-2 rep and cap genes under the control
20 of a homologous P5 promoter. This cell line is characterized by integration into the cellular chromosome of multiple copies (at least 5 copies) of P5-rep-cap gene cassettes in a concatomer form. This B-50 cell line was deposited with the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209, on September 18, 1997 under Accession No. CRL-12401 pursuant to the
25 provisions of the Budapest Treaty. However, the present invention is not limited as to the selection of the packaging cell line.

Exemplary transducing vectors based on AAV-1 capsid proteins have been tested both *in vivo* and *in vitro*, as described in more detail in Example 4. In these studies, it was demonstrated that recombinant AAV vector with an AAV-1
30 virion can transduce both mouse liver and muscle. These, and other AAV-1 based

gene therapy vectors which may be generated by one of skill in the art are beneficial for gene delivery to selected host cells and gene therapy patients since the neutralization antibodies of AAV-1 present in much of the human population exhibit different patterns from other AAV serotypes and therefore do not neutralize the AAV-1 virions. One of skill in the art may readily prepare other rAAV viral vectors containing the AAV-1 capsid proteins provided herein using a variety of techniques known to those of skill in the art. One may similarly prepare still other rAAV viral vectors containing AAV-1 sequence and AAV capsids of another serotype.

B. Other Viral Vectors

One of skill in the art will readily understand that the AAV-1 sequences of the invention can be readily adapted for use in these and other viral vector systems for *in vitro*, *ex vivo* or *in vivo* gene delivery. Particularly well suited for use in such viral vector systems are the AAV-1 ITR sequences, the AAV-1 rep, the AAV-1 cap, and the AAV-1 P5 promoter sequences.

For example, in one desirable embodiment, the AAV-1 ITR sequences of the invention may be used in an expression cassette which includes AAV-1 5' ITR, a non-AAV DNA sequences of interest (e.g., a minigene), and 3' ITR and which lacks functional rep/cap. Such a cassette containing an AAV-1 ITR may be located on a plasmid for subsequent transfection into a desired host cell, such as the cis plasmid described above. This expression cassette may further be provided with an AAV capsid of a selected serotype to permit infection of a cell or stably transfected into a desired host cell for packaging of rAAV virions. Such an expression cassette may be readily adapted for use in other viral systems, including adenovirus systems and lentivirus systems. Methods of producing Ad/AAV vectors are well known to those of skill in the art. One desirable method is described in PCT/US95/14018. However, the present invention is not limited to any particular method.

Another aspect of the present invention is the novel AAV-1 P5 promoter sequences which are located in the region spanning nt 236 - 299 of SEQ ID NO: 1. This promoter is useful in a variety of viral vectors for driving expression of a desired transgene.

Similarly, one of skill in the art can readily select other fragments of the AAV-1 genome of the invention for use in a variety of vector systems. Such vectors systems may include, e.g., lentiviruses, retroviruses, poxviruses, vaccinia viruses, and adenoviral systems, among others. Selection of these vector systems is not a
5 limitation of the present invention.

C. Host Cells And Packaging Cell Lines

In yet another aspect, the present invention provides host cells which may be transiently transfected with AAV-1 nucleic acid sequences of the invention to permit expression of a desired transgene or production of a rAAV particle. For
10 example, a selected host cell may be transfected with the AAV-1 P5 promoter sequences and/or the AAV-1 5' ITR sequences using conventional techniques. Providing AAV helper functions to the transfected cell lines of the invention results in packaging of the rAAV as infectious rAAV particles. Such cell lines may be produced in accordance with known techniques [see, e.g., US Patent No. 5,658,785], making
15 use of the AAV-1 sequences of the invention.

Alternatively, host cells of the invention may be stably transfected with a rAAV expression cassette of the invention, and with copies of AAV-1 rep and cap genes. Suitable parental cell lines include mammalian cell lines and it may be desirable to select host cells from among non-simian mammalian cells. Examples of suitable
20 parental cell lines include, without limitation, HeLa [ATCC CCL 2], A549 [ATCC Accession No. CCL 185], KB [CCL 17], Detroit [e.g., Detroit 510, CCL 72] and WI-38 [CCL 75] cells. These cell lines are all available from the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209 USA. Other suitable parent cell lines may be obtained from other sources and may be used to
25 construct stable cell lines containing the P5 and/or AAV rep and cap sequences of the invention.

Recombinant vectors generated as described above are useful for delivery of the DNA of interest to cells.

III. METHODS OF DELIVERING GENES VIA AAV-1 DERIVED VECTORS

In another aspect, the present invention provides a method for delivery of a transgene to a host which involves transfecting or infecting a selected host cell with a recombinant viral vector generated with the AAV-1 sequences (or functional
5 fragments thereof) of the invention. Methods for delivery are well known to those of skill in the art and are not a limitation of the present invention.

In one desirable embodiment, the invention provides a method for AAV--mediated delivery of a transgene to a host. This method involves transfecting or infecting a selected host cell with a recombinant viral vector containing a selected
10 transgene under the control of sequences which direct expression thereof and AAV-1 capsid proteins.

Optionally, a sample from the host may be first assayed for the presence of antibodies to a selected AAV serotype. A variety of assay formats for detecting neutralizing antibodies are well known to those of skill in the art. The selection of
15 such an assay is not a limitation of the present invention. See, e.g., Fisher et al, Nature Med., 3(3):306-312 (March 1997) and W. C. Manning et al, Human Gene Therapy, 9:477-485 (March 1, 1998). The results of this assay may be used to determine which AAV vector containing capsid proteins of a particular serotype are preferred for delivery, e.g., by the absence of neutralizing antibodies specific for that
20 capsid serotype.

In one aspect of this method, the delivery of vector with AAV-1 capsid proteins may precede or follow delivery of a gene via a vector with a different serotype AAV capsid protein. Thus, gene delivery via rAAV vectors may be used for repeat gene delivery to a selected host cell. Desirably, subsequently administered
25 rAAV vectors carry the same transgene as the first rAAV vector, but the subsequently administered vectors contain capsid proteins of serotypes which differ from the first vector. For example, if a first vector has AAV-2 capsid proteins, subsequently administered vectors may have capsid proteins selected from among the other serotypes, including AAV-1, AAV-3A, AAV-3B, AAV-4 and AAV-6.

Thus, a rAAV-1-derived recombinant viral vector of the invention provides an efficient gene transfer vehicle which can deliver a selected transgene to a selected host cell *in vivo* or *ex vivo* even where the organism has neutralizing antibodies to one or more AAV serotypes. These compositions are particularly well suited to gene
5 delivery for therapeutic purposes. However, the compositions of the invention may also be useful in immunization. Further, the compositions of the invention may also be used for production of a desired gene product *in vitro*.

The above-described recombinant vectors may be delivered to host cells according to published methods. An AAV viral vector bearing the selected transgene
10 may be administered to a patient, preferably suspended in a biologically compatible solution or pharmaceutically acceptable delivery vehicle. A suitable vehicle includes sterile saline. Other aqueous and non-aqueous isotonic sterile injection solutions and aqueous and non-aqueous sterile suspensions known to be pharmaceutically acceptable carriers and well known to those of skill in the art may be employed for
15 this purpose.

The viral vectors are administered in sufficient amounts to transfect the cells and to provide sufficient levels of gene transfer and expression to provide a therapeutic benefit without undue adverse effects, or with medically acceptable physiological effects, which can be determined by those skilled in the medical arts.
20 Conventional and pharmaceutically acceptable routes of administration include, but are not limited to, direct delivery to the liver, oral, intranasal, intravenous, intramuscular, subcutaneous, intradermal, and other parental routes of administration. Routes of administration may be combined, if desired.

Dosages of the viral vector will depend primarily on factors such as the
25 condition being treated, the age, weight and health of the patient, and may thus vary among patients. For example, a therapeutically effective human dosage of the viral vector is generally in the range of from about 1 ml to about 100 ml of solution containing concentrations of from about 1×10^9 to 1×10^{16} genomes virus vector. A preferred human dosage may be about 1×10^{13} to 1×10^{16} AAV genomes. The
30 dosage will be adjusted to balance the therapeutic benefit against any side effects and

such dosages may vary depending upon the therapeutic application for which the recombinant vector is employed. The levels of expression of the transgene can be monitored to determine the frequency of dosage resulting in viral vectors, preferably AAV vectors containing the minigene. Optionally, dosage regimens similar to those described for therapeutic purposes may be utilized for immunization using the compositions of the invention. For *in vitro* production, a desired protein may be obtained from a desired culture following transfection of host cells with a rAAV containing the gene encoding the desired protein and culturing the cell culture under conditions which permits expression. The expressed protein may then be purified and isolated, as desired. Suitable techniques for transfection, cell culturing, purification, and isolation are known to those of skill in the art.

The following examples illustrate several aspects and embodiments of the invention.

Example 1 - Generation of Infectious Clone of AAV-1

The replicated form DNA of AAV-1 was extracted from 293 cells that were infected by AAV-1 and wild type adenovirus type 5.

A. Cell Culture and Virus

AAV-free 293 cells and 84-31 cells were provided by the human application laboratory of the University of Pennsylvania. These cells were cultured in Dulbecco's Modified Eagle Medium with 10% fetal bovine serum (Hyclone), penicillin (100 U/ml) and streptomycin at 37°C in a moisturized environment supplied with 5% CO₂. The 84-31 cell line constitutively expresses adenovirus genes E1a, E1b, E4/ORF6, and has been described previously [K. J. Fisher, *J. Virol.*, 70:520-532 (1996)]. AAV-1 (ATCC VR-645) seed stock was purchased from American Type Culture Collection (ATCC, Manassas, VA). AAV viruses were propagated in 293 cells with wild type Ad5 as a helper virus.

B. Recombinant AAV Generation

The recombinant AAV viruses were generated by transfection using an adenovirus free method. Briefly, the cis plasmid (with AAV ITR), trans plasmid (with

AAV rep gene and cap gene) and helper plasmid (pFΔ13, with essential regions from the adenovirus genome) were simultaneously co-transfected into 293 cells in a ratio of 1:1:2 by calcium phosphate precipitation. The pFΔ13 helper plasmid has an 8 kb deletion in the adenovirus E2B region and has deletions in most of the late genes.

5 This helper plasmid was generated by deleting the RsrII fragment from pFG140 (Microbix, Canada). Typically, 50 μg of DNA (cis:trans:PFΔ13 at ratios of 1:1:2, respectively) was transfected onto a 15 cm tissue culture dish. The cells were harvested 96 hours post-transfection, sonicated and treated with 0.5% sodium deoxycholate (37°C for 10 min). Cell lysates were then subjected to two rounds of a

10 CsCl gradient. Peak fractions containing AAV vector were collected, pooled, and dialyzed against PBS before injecting into animals. To make rAAV virus with AAV-1 virion, the pAV1H or p5E18 (2/1) was used as the *trans* plasmid to provide rep and cap function.

For the generation of rAAV based on AAV-2, p5E18 was used as the

15 *trans* plasmid since it greatly improved the rAAV yield. This plasmid, p5E18(2/2), expresses AAV-2 Rep and Cap and contains a P5 promoter relocated to a position 3' to the Cap gene, thereby minimizing expression of Rep78 and Rep68. The strategy was initially described by Li et al, *J. Virol.*, 71:5236-5243 (1997). P5E18(2/2) was constructed in the following way. The previously described pMMTV-*trans* vector

20 (i.e., the mouse mammary tumor virus promoter substituted for the P5 promoter in an AAV-2-based vector) was digested with *Sma*I and *Cla*I, filled in with the Klenow enzyme, and then recircularized with DNA ligase. The resulting construct was digested with *Xba*I, filled in, and ligated to the blunt-ended BamHI-*Xba*I fragment from pCR-p5, constructed in the following way. The P5 promoter of AAV was

25 amplified by PCR and the amplified fragment was subsequently cloned into pCR2.1 (Invitrogen) to yield pCR-P5. The helper plasmid pAV1H was constructed by cloning the *Bfa*I fragment of pAAV-2 into pBluescript II-SK(+) at the *Bco*rV and *Sma*I sites. The 3.0-kb *Xba*I-*Kpn*I fragment from p5E18(2/2), the 2.3-kb *Xba*I-*Kpn*I fragment from pAV1H, and the 1.7-kb *Kpn*I fragment from p5E18(2/2) were incorporated into

30 a separate plasmid P5E18(2/1), which contains AAV-2 Rep, AAV-1 Cap, and the

AAV-2 P5 promoter located 3' to the Cap gene. Plasmid p5E18(2/1) produced 10- to 20-fold higher quantities of the vector than pAV1H (i.e., 10^{12} genomes/50 15-cm² plates).

C. DNA Techniques

5 Hirt DNA extraction was performed as described in the art with minor modification [R.J. Samulski et al., Cell, 33:135-143 (1983)]. More particularly, Hirt solution without SDS was used instead of using original Hirt solution containing SDS. The amount of SDS present in the original Hirt solution was added after the cells had been fully suspended. To construct AAV-1 infectious clone, the Hirt DNA from
10 AAV-1 infected 293 cells was repaired with Klenow enzyme (New England Biolabs) to ensure the ends were blunt. The treated AAV-1 Hirt DNA was then digested with *Bam*HI and cloned into three vectors, respectively. The internal *Bam*HI was cloned into pBlueScript II-SK+ cut with *Bam*HI to get pAV1-BM. The left and right fragments were cloned into pBlueScript II-SK+ cut with *Bam*HI + EcoRV to obtain
15 pAV1-BL and pAV1-BR, respectively. The AAV sequence in these three plasmids were subsequently assembled into the same vector to get AAV-1 infectious clone pAAV-1. The helper plasmid for recombinant AAV-1 virus generation was constructed by cloning the Bfa I fragment of pAAV-1 into pBlueScript II-SK+ at the EcoRV site.

20 Analysis of the Hirt DNA revealed three bands, a dimer at 9.4 kb, a monomer at 4.7 kb and single-stranded DNA at 1.7 kb, which correlated to different replication forms of AAV-1. The monomer band was excised from the gel and then digested with *Bam*HI. This resulted in three fragments of 1.1 kb, 0.8 kb and 2.8 kb. This pattern is in accordance with the description by Bantel-schaal and zur Hausen,
25 Virology, 134(1):52-63 (1984). The 1.1 kb and 2.8 kb *Bam*HI fragments were cloned into pBlueScript-KS(+) at *Bam*HI and EcoRV site. The internal 0.8 kb fragment was cloned into *Bam*HI site of pBlueScript-KS(+).

These three fragments were then subcloned into the same construct to obtain a plasmid (pAAV-1) that contained the full sequence of AAV-1. The pAAV-1
30 was then tested for its ability to rescue from the plasmid backbone and package

infectious virus. The pAAV-1 was then transfected to 293 cells and supplied with adenovirus type as helper at MOI 10. The virus supernatant was used to reinfect 293 cells.

For Southern blot analysis, Hirt DNA was digested with *DpnI* to
5 remove bacteria-borne plasmid and probed with internal *BamHI* fragment of AAV-1. The membrane was then washed at high stringency conditions, which included: twice 30 minutes with 2X SSC, 0.1% SDS at 65°C and twice 30 minutes with 0.1X SSC, 0.1% SDS at 65°C. The membrane was then analyzed by both phosphor image and X-ray autoradiography. The results confirmed that pAAV-1 is indeed an infectious
10 clone of AAV serotype 1.

Example 2 - Sequencing Analysis of AAV-1

The entire AAV-1 genome was then determined by automatic sequencing and was found to be 4718 nucleotides in length (Figs. 1A-1C). For sequencing, an ABI 373 automatic sequencer as used to determine the sequences for all plasmids and PCR
15 fragments related to this study using the FS dye chemistry. All sequences were confirmed by sequencing both plus and minus strands. These sequences were also confirmed by sequencing two independent clones of pAV-BM, pAV-BL and pAV-BR. Since the replicated form of AAV-1 DNA served as the template for sequence determination, these sequences were also confirmed by sequencing a series of PCR
20 products using original AAV-1 seed stock as a template.

The length of AAV-1 was found to be within the range of the other serotypes: AAV-3 (4726 nucleotides), AAV-4 (4774 nucleotides), AAV-2 (4681 nucleotides), and AAV-6 (4683 nucleotides).

The AAV-1 genome exhibited similarities to other serotypes of adeno-
25 associated viruses. Overall, it shares more than 80% identity with other known AAV viruses as determined by the computer program Megalign using default settings [DNASTAR, Madison, WI]. The key features in AAV-2 can also be found in AAV-1. First, AAV-1 has the same type of inverted terminal repeat which is capable of forming T-shaped hairpin structures, despite the differences at the nucleotide level

(Figs. 2 and 3). The sequences of right ITRs and left ITRs of AAV-1 are identical. The AAV TR sequence is subdivided into A, A', B, B', C, C', D and D' [Bern, cited above].

These AAV ITR sequences are also virtually the same as those found in AAV-6 right ITR, there being one nucleotide difference in each of A and A' sequence, and the last nucleotide of the D sequence. Second, the AAV-2 rep binding motif [GCTCGCTCGCTCGCTG (SEQ ID NO: 20)] is well conserved. Such motif can also be found in the human chromosome 19 AAV-2 pre-integration region. Finally, non-structural and structural coding regions, and regulatory elements similar to those of other AAV serotypes also exist in AAV-1 genome.

Although the overall features of AAV terminal repeats are very much conserved, the total length of the AAV terminal repeat exhibits divergence. The terminal repeat of AAV-1 consists of 143 nucleotides while those of AAV-2, AAV-3, and AAV-4 are about 145 or 146 nucleotides. The loop region of AAV-1 ITR most closely resembles that of AAV-4 in that it also uses TCT instead of the TTT found in AAV-2 and AAV-3. The possibility of sequencing error was eliminated using restriction enzyme digestion, since these three nucleotides are part of the SacI site (gagctc; nt 69-74 of SEQ ID NO: 1). The p5 promoter region of AAV-1 shows more variations in nucleotide sequences with other AAV serotypes. However, it still maintains the critical regulatory elements. The two copies of YY1 [See, Fig. 1A-1C] sites seemed to be preserved in all known AAV serotypes, which have been shown to be involved in regulating AAV gene expression. In AAV-4, there are 56 additional nucleotides inserted between YY1 and E-box/USF site, while in AAV-1, there are 26 additional nucleotides inserted before the E-box/USF site. The p19 promoter, p40 promoter and polyA can also be identified from the AAV-1 genome by analogy to known AAV serotypes, which are also highly conserved.

Thus, the analysis of AAV terminal repeats of various serotypes showed that the A and A' sequence is very much conserved. One of the reasons may be the Rep binding motif (GCTC)₃GCTG [SEQ ID NO: 20]. These sequences appear to be essential for AAV DNA replication and site-specific integration. The same sequence

has also been shown to be preserved in a monkey genome [Samulski, personal communication]. The first 8 nucleotides of the D sequence are also identical in all known AAV serotypes. This is in accordance with the observation of the Srivastava group that only the first 10 nucleotides are essential for AAV packaging [X.S. Wang et al, *J. Virol.*, 71:3077-3082 (1997); X.S. Wang et al, *J. Virol.*, 71:1140-1146 (1997)]. The function of the rest of the D sequences still remain unclear. They may be somehow related to their tissue specificities. The variation of nucleotide in B and C sequence may also suggest that the secondary structure of the ITRs is more critical for its biological function, which has been demonstrated in many previous publications.

Example 3 - Comparison of AAV-1 Sequences

The nucleotide sequences of AAV-1, obtained as described above, were compared with known AAV sequences, including AAV-2, AAV-4 and AAV-6 using DNA Star Megalign. This comparison revealed a stretch of 71 identical nucleotides shared by AAV-1, AAV-2 and AAV-6. See, Figs. 1A-1C.

This comparison further suggested that AAV-6 is a hybrid formed by homologous recombination of AAV-1 and AAV-2. See, Figs. 3A and 3B. These nucleotides divide the AAV-6 genome into two regions. The 5' half of AAV-6 of 522 nucleotides is identical to that of AAV-2 except in 2 positions. The 3' half of AAV-6 including the majority of the rep gene, complete cap gene and 3' ITR is 98% identical to AAV-1.

Biologically, such recombination may enable AAV-1 to acquire the ability to transmit through the human population. It is also interesting to note that the ITRs of AAV-6 comprise one AAV-1 ITR and one AAV-2 ITR. The replication model of defective parvovirus can maintain this special arrangement. Studies on AAV integration have shown that a majority of AAV integrants carries deletions in at least one of the terminal repeats. These deletions have been shown to be able to be repaired through gene conversion using the other intact terminal repeat as a template. Therefore, it would be very difficult to maintain AAV-6 as a homogenous population

when an integrated copy of AAV-6 is rescued from host cells with helper virus infection. The AAV-6 with two identical AAV-2 ITRs or two identical AAV-1 ITRs should be the dominant variants. The AAV-6 with two AAV-1 ITRs has been observed by Russell's group [Rutledge, cited above (1998)]. So far there is no report
5 on AAV-6 with two AAV-2 ITRs. Acquisition of AAV-2 P5 promoter by AAV-6 may have explained that AAV-6 have been isolated from human origin while AAV-1 with the same virion has not. The regulation of P5 promoter between different species of AAV may be different *in vivo*. This observation suggests the capsid proteins of AAV were not the only determinants for tissue specificity.

10 Although it is clear that AAV-6 is a hybrid of AAV-1 and AAV-2, AAV-6 has already exhibited divergence from either AAV-1 or AAV-2. There are two nucleotide differences between AAV-6 and AAV-2 in their first 450 nucleotides. There are about 1% differences between AAV-6 and AAV-1 in nucleotide levels from nucleotides 522 to the 3' end. There also exists a quite divergent region (nucleotide
15 4486-4593) between AAV-6 and AAV-1 (Figs. 1A-1C). This region does not encode any known proteins for AAVs. These differences in nucleotide sequences may suggest that AAV-6 and AAV-1 have gone through some evolution since the recombination took place. Another possible explanation is that there exists another variant of AAV-1 which has yet to be identified. So far, there is no evidence to rule
20 out either possibility. It is still unknown if other hybrids (AAV-2 to AAV-4, etc.) existed in nature.

The coding region of AAV-1 was deduced by comparison with other known AAV serotypes. Table 1 illustrates the coding region differences between AAV-1 and AAV-6. The amino acid residues are deduced according to AAV-2.

25 With reference to the amino acid position of AAV-1, Table 1 lists the amino acids of AAV-1 which have been changed to the corresponding ones of AAV-6. The amino acids of AAV-1 are shown to the left of the arrow. Reference may be made to SEQ ID NO: 5 of the amino acid sequence of AAV-1 Rep 78 and to SEQ ID NO: 13 for the amino acid sequence of AAV-1 VP1.

Table 1

Coding region variations between AAV-1 and AAV-6

Rep protein (Rep78)			Cap protein (VP1)	
Position(s)	Amino acids		Position(s)	Amino acids
28	S-N		129	L-F
191	Q-H		418	E-D
192	H-D		531	E-K
308	E-D		584	F-L
			598	A-V
			642	N-H

It was surprising to see that the sequence of the AAV-1 coding region is almost identical to that of AAV-6 from position 452 to the end of coding region (99%). The first 508 nucleotides of AAV-6 have been shown to be identical to those of AAV-2 [Rutledge, cited above (1998)]. Since the components of AAV-6 genome seemed to be AAV-2 left ITR – AAV-2 p5 promoter – AAV-1 coding region – AAV-1 right ITR, it was concluded that AAV-6 is a naturally occurred hybrid between AAV-1 and AAV-2.

Example 4 - Gene Therapy Vector Based on AAV-1

Recombinant gene transfer vectors based on AAV-1 viruses were constructed by the methods described in Example 1. To produce a hybrid recombinant virus with AAV-1 virion and AAV-2 ITR, the AAV-1 trans plasmid (pAV1H) and the AAV-2 cis-lacZ plasmid (with AAV-2 ITR) were used. The AAV-2 ITR was used in this vector in view of its known ability to direct site-specific integration. Also constructed for use in this experiment was an AAV-1 vector carrying the green fluorescent protein (GFP) marker gene under the control of the immediate early promoter of CMV using pAV1H as the trans plasmid.

A. rAAV-1 Viruses Transfect Host Cells in Vitro

84-31 cells, which are subclones of 293 cells (which express adenovirus E1a, E1b) which stably express E4/ORF5, were infected with rAAV-1 GFP or rAAV-lacZ. High levels of expression of GFP and lacZ was detected in the
5 cultured 84-31 cells. This suggested that rAAV-1 based vector was very similar to AAV-2 based vectors in ability to infect and expression levels.

B. rAAV-1 Viruses Transfect Cells in Vivo

The performance of AAV-1 based vectors was also tested *in vivo*. The rAAV-1 CMV- α 1AT virus was constructed as follows. The EcoRI fragment of
10 pAT85 (ATCC) containing human α 1-antitrypsin (α 1AT) cDNA fragment was blunted and cloned into PCR (Promega) at a SmaI site to obtain PCR- α 1AT. The CMV promoter was cloned into PCR- α 1AT at the XbaI site. The Alb- α 1AT expression cassette was removed by XhoI and ClaI and cloned into pAV1H at the XbaI site. This vector plasmid was used to generate AAV-1-CMV- α 1AT virus used
15 in the experiment described below.

For screening human antibodies against AAV, purified AAV virus is lysed with RIPA buffer (10 mM Tris pH 8.2, 1% Triton X-100, 1% SDS, 0.15 M NaCl) and separated in 10% SDS-PAGE gel. The heat inactivated human serum was used at a 1 to 1000 dilution in this assay. The rAAV-1 CMV- α 1AT viruses were
20 injected into Rag-1 mice through tail vein injection at different dosages. The concentration of human α 1-antitrypsin in mouse serum was measured using ELISA. The coating antibody is rabbit anti-human human α 1-antitrypsin (Sigma). The goat-antihuman α 1-antitrypsin (Sigma) was used as the primary detection antibodies. The sensitivity of this assay is around 0.3 ng/ml to 30 ng/ml. The expression of human α -
25 antitrypsin in mouse blood can be detected in a very encouraging level. This result is shown in Table 2.

Table 2

Human Antitrypsin Expressed in Mouse Liver

Amount of virus injected	Week 2 (ng/ml)	Week 4 (ng/ml)
2x10 ¹⁰ genomes	214.2	171.4
1x10 ¹⁰ genomes	117.8	109.8
5x10 ¹⁰ genomes	64.5	67.8
2.5x10 ¹⁰ genomes	30.9	58.4

5
10
that AAV-1 based vector would be appropriate for both liver and muscle gene delivery.

Example 5 - Neutralizing Antibodies Against AAV-1

Simple and quantitative assays for neutralizing antibodies (NAB) to AAV-1 and AAV-2 were developed with recombinant vectors. A total of 33 rhesus monkeys
15 and 77 normal human subjects were screened.

A. Nonhuman Primates

Wild-caught juvenile rhesus monkeys were purchased from Covance (Alice, Tex.) and LABS of Virginia (Yemassee, SC) and kept in full quarantine. The monkeys weighed approximately 3 to 4 kg. The nonhuman primates used in the
20 Institute for Human Gene Therapy research program are purposefully bred in the United States from specific-pathogen-free closed colonies. All vendors are US Department of Agriculture class A dealers. The rhesus macaques are therefore not infected with important simian pathogens, including the tuberculosis agent, major simian lentiviruses (simian immunodeficiency virus and simian retroviruses), and
25 cercopithecine herpesvirus. The animals are also free of internal and external parasites. The excellent health status of these premium animals minimized the potential for extraneous variables. For this study, serum was obtained from monkeys prior to initiation of any protocol.

NAB titers were analyzed by assessing the ability of serum antibody to inhibit the transduction of reporter virus expressing green fluorescent protein (GFP) (AAV1-GFP or AAV2-GFP) into 84-31 cells. Various dilutions of antibodies preincubated with reporter virus for 1 hour at 37°C were added to 90% confluent cell
5 cultures. Cells were incubated for 48 hours and the expression of green fluorescent protein was measured by FluoroImaging (Molecular Dynamics). NAB titers were calculated as the highest dilution at which 50% of the cells stained green.

Analysis of NAB in rhesus monkeys showed that 61% of animals tested positive for AAV-1; a minority (24%) has NAB to AAV-2. Over one-third of
10 animals had antibodies to AAV-1 but not AAV-2 (i.e., were monospecific for AAV-1), whereas no animals were positive for AAV-2 without reacting to AAV-1. These data support the hypothesis that AAV-1 is endemic in rhesus monkeys. The presence of true AAV-2 infections in this group of nonhuman primates is less clear, since cross-neutralizing activity of an AAV-1 response to AAV-2 can not be ruled out. It is
15 interesting that there is a linear relationship between AAV-2 NAB and AAV-1 NAB in animals that had both.

B. *Humans*

For these neutralization antibody assays, human serum samples were incubated at 56°C for 30 min to inactivate complement and then diluted in DMEM.
20 The virus (rAAV or rAd with either lacZ or GFP) was then mixed with each serum dilution (20X, 400X, 2000X, 4000X, etc.) and incubated for 1 hour at 37°C before applied to 90% confluent cultures of 84-31 cells (for AAV) or HeLa cells (for adenovirus) in 96-well plates. After 60 minutes of incubation at culture condition, 100 µl additional media containing 20% FCS was added to make final culture media
25 containing 10% FCS.

The result is summarized in Table 3.

Table 3

Adenovirus	AAV-1	AAV-2	# of samples	Percentage
-	-	-	41	53.2%
+	-	-	16	20.8%
-	+	-	0	0.0%
-	-	+	2	2.6%
-	+	+	2	2.6%
+	-	+	3	3.9%
+	+	-	0	0.0%
+	+	+	13	16.9%
Total			77	100%

The human neutralizing antibodies against these three viruses seemed to be unrelated since the existence of neutralizing antibodies against AAV are not indications for antibodies against adenovirus. However, AAV requires adenovirus as helper virus, in most of the cases, the neutralizing antibodies against AAV correlated with the existence of neutralizing antibodies to adenovirus. Among the 77 human serum samples screened, 41% of the samples can neutralize the infectivity of recombinant adenovirus based on Ad5. 15/77 (19%) of serum samples can neutralize the transduction of rAAV-1 while 20/77 (20%) of the samples inhibit rAAV-2 transduction at 1 to 80 dilutions or higher. All serum samples positive in neutralizing antibodies for AAV-1 in are also positive for AAV-2. However, there are five (6%) rAAV-2 positive samples that failed to neutralize rAAV-1. In samples that are positive for neutralizing antibodies, the titer of antibodies also varied in the positive ones. The results from screening human sera for antibodies against AAVs supported the conclusion that AAV-1 presents the same epitome as that of AAV-2 to interact

with cellular receptors since AAV-1 neutralizing human serums can also decrease the infectivity of AAV-2. However, the profile of neutralizing antibodies for these AAVs is not identical, there are additional specific receptors for each AAV serotype.

Example 6 - Recombinant AAV Viruses Exhibit Tissue Tropism

5 The recombinant AAV-1 vectors of the invention and the recombinant AAV-2 vectors [containing the gene encoding human α 1-antitrypsin (α 1AT) or murine erythropoietin (Epo) from a cytomegalovirus-enhanced β -actin promoter (CB)] were evaluated in a direct comparison to equivalent copies of AAV-2 vectors containing the same vector genes.

10 Recombinant viruses with AAV-1 capsids were constructed using the techniques in Example 1. To make rAAV with AAV-1 virions, pAV1H or p5E18 (2/1) was used as the *trans* plasmid to provide Rep and Cap functions. For the generation of the rAAV based on AAV-2, p5E18(2/2) was used as the *trans* plasmid, since it greatly improved the rAAV yield. [Early experiments indicated similar *in vivo*
15 performances of AAV-1 vectors produced with pAV1H and p5E19 (2/1). All subsequent studies used AAV-1 vectors derived from p5E18(2/1) because of the increased yield.]

 Equivalent stocks of the AAV-1 and AAV-2 vectors were injected intramuscularly (5×10^{10} genomes) or liver via the portal circulation (1×10^{11}
20 genomes) into immunodeficient mice, and the animals (four groups) were analyzed on day 30 for expression of transgene. See, Figs. 4A and 4B.

 AAV-2 vectors consistently produced 10- to 50-fold more serum erythropoietin or α 1-antitrypsin when injected into liver compared to muscle. (However, the AAV-1-delivered genes did achieve acceptable expression levels in the
25 liver.) This result was very different from that for AAV-1 vectors, with which muscle expression was equivalent to or greater than liver expression. In fact, AAV-1 outperformed AAV-2 in muscle when equivalent titers based on genomes were administered.

Example 7 - Gene Delivery via rAAV-1

C57BL/6 mice (6- to 8-week old males, Jackson Laboratories) were analyzed for AAV mediated gene transfer to liver following intrasplenic injection of vector (i.e., targeted to liver). A total of 10^{11} genome equivalents of rAAV-1 or rAAV-2 vector
5 were injected into the circulation in 100 μ l buffered saline. The first vector contained either an AAV-1 capsid or an AAV-2 capsid and expressed α 1AT under the control of the chicken β -actin (CB) promoter. Day 28 sera were analyzed for antibodies against AAV-1 or AAV-2 and serum α 1AT levels were checked. Animals were then injected with an AAV-1 or AAV-2 construct expressing erythropoietin (Epo, also under the
10 control of the CB promoter). One month later sera was analyzed for serum levels of Epo. The following groups were analyzed (Figs. 5A-5D).

In Group 1, vector 1 was AAV-2 expressing α 1AT and vector 2 was AAV-2 expressing Epo. Animals generated antibodies against AAV-2 following the first vector administration which prevented the readministration of the AAV-2 based
15 vector. There was no evidence for cross-neutralizing the antibody to AAV-1.

In Group 2, vector 1 was AAV-1 expressing α 1AT while vector 2 was AAV-1 expressing Epo. The first vector administration did result in significant α 1AT expression at one month associated with antibodies to neutralizing antibodies to AAV-1. The animals were not successfully readministered with the AAV-1 Epo
20 expressing construct.

In Group 3, the effectiveness of an AAV-2 vector expressing Epo injected into a naive animal was measured. The animals were injected with PBS and injected with AAV-2 Epo vector at day 28 and analyzed for Epo expression one month later. The neutralizing antibodies were evaluated at day 28 so we did not expect to see anything
25 since they received PBS with the first vector injection. This shows that in naive animals AAV-2 is very efficient at transferring the Epo gene as demonstrated by high level of serum Epo one month later.

Group 4 was an experiment similar to Group 3 in which the animals originally received PBS for vector 1 and then the AAV-1 expressing Epo construct 28 days
30 later. At the time of vector injection, there obviously were no antibodies to either

AAV-1 or AAV-2. The AAV-1 based vector was capable of generating significant expression of Epo when measured one month later.

Group 5 is a cross-over experiment where the initial vector is AAV-2 expressing α 1AT followed by the AAV-1 construct expressing Epo. The animals, as expected, were efficiently infected with the AAV-2 vector expressing α 1AT as shown by high levels of the protein in blood at 28 days. This was associated with significant neutralizing antibodies to AAV-2. Importantly, the animals were successfully administered AAV-1 following the AAV-2 vector as shown by the presence of Epo in serum 28 days following the second vector administration. At the time of this vector administration, there was high level AAV-2 neutralizing antibodies and very low cross-reaction to AAV-1. The level of Epo was slightly diminished possibly due to a small amount of cross-reactivity. Group 6 was the opposite cross-over experiment in which the initial vector was AAV-1 based, whereas the second experiment was AAV-2 based. The AAV-1 vector did lead to significant gene expression of α 1AT, which also resulted in high level AAV-1 neutralizing antibody. The animals were very efficiently administered AAV-2 following the initial AAV-1 vector as evidenced by high level Epo.

A substantially identical experiment was performed in muscle in which 5×10^{10} genomes were injected into the tibialis anterior of C57BL/6 mice as a model for muscle directed gene therapy. The results are illustrated in Figs. 6A-6D and are essentially the same as for liver.

In summary, this experiment demonstrates the utility of using an AAV-1 vector in patients who have pre-existing antibodies to AAV-2 or who had initially received an AAV-2 vector and need readministration.

25 Example 8 - Construction of Recombinant Viruses Containing AAV-1 ITRs

This example illustrates the construction of recombinant AAV vectors which contain AAV-1 ITRs of the invention.

An AAV-1 cis plasmid is constructed as follows. A 160 bp Xho-NruI AAV-1 fragment containing the AAV-1 5' ITR is obtained from pAV1-BL. pAV1-BL was

generated as described in Example 1. The Xho-NruI fragment is then cloned into a second pAV1-BL plasmid at an XbaI site to provide the plasmid with two AAV-1 ITRs. The desired transgene is then cloned into the modified pAV-1BL at the NruI and BamHI site, which is located between the AAV-1 ITR sequences. The resulting
5 AAV-1 cis plasmid contains AAV-1 ITRs flanking the transgene and lacks functional AAV-1 rep and cap.

Recombinant AAV is produced by simultaneously transfecting three plasmids into 293 cells. These include the AAV-1 cis plasmid described above; a trans plasmid which provides AAV rep/cap functions and lacks AAV ITRs; and a plasmid providing
10 adenovirus helper functions. The rep and/or cap functions may be provided in trans by AAV-1 or another AAV serotype, depending on the immunity profile of the intended recipient. Alternatively, the rep or cap functions may be provided in cis by AAV-1 or another serotype, again depending on the patient's immunity profile.

In a typical cotransfection, 50 µg of DNA (cis:trans:helper at ratios of 1:1:2, respectively) is transfected onto a 15 cm tissue culture dish. Cells are harvested 96
15 hours post transfection, sonicated and treated with 0.5% sodium deoxycholate (37° for 10 min). Cell lysates are then subjected to 2-3 rounds of ultracentrifugation in a cesium gradient. Peak fractions containing rAAV are collected, pooled and dialyzed against PBS. A typical yield is 1×10^{13} genomes/ 10^9 cells.

20 Using this method, one recombinant virus construct is prepared which contains the AAV-1 ITRs flanking the transgene, with an AAV-1 capsid. Another recombinant virus construct is prepared with contains the AAV-1 ITRs flanking the transgene, with an AAV-2 capsid.

All publications cited in this specification are incorporated herein by reference.
25 While the invention has been described with reference to a particularly preferred embodiment, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the claims.

What is claimed is:

1. An isolated AAV-1 nucleic acid molecule comprising a sequence selected from the group consisting of:
 - (a) SEQ ID NO: 1;
 - (b) a DNA sequence complementary to SEQ ID NO: 1;
 - (c) cDNA complementary to (a) or (b); and
 - (d) RNA complementary to any of (a) to (c).
2. A nucleic acid molecule comprising an AAV-1 inverted terminal repeat (ITR) sequence selected from the group consisting of:
 - (a) nt 1 to 143 of SEQ ID NO: 1;
 - (b) nt 4576 to 4718 of SEQ ID NO: 1;
 - (c) a nucleic acid sequence complementary to (a) or (b); and
 - (d) a functional fragment of (a), (b), or (c).
3. A recombinant vector comprising a 5' AAV-1 inverted terminal repeat (ITR) and a selected transgene, wherein said ITR has the sequence selected from the group consisting of:
 - (a) nt 1 to 143 of SEQ ID NO: 1;
 - (b) a nucleic acid sequence complementary to (a); and
 - (c) a functional fragment of (a) or (b).
4. The recombinant vector according to claim 3, wherein said vector further comprises a 3' AAV-1 ITR.

5. A recombinant vector comprising a 3' AAV-1 inverted terminal repeat (ITR) and a selected transgene, wherein said ITR has the sequence selected from the group consisting of:

- (a) nt 4576 to 4718 of SEQ ID NO: 1;
- (b) a nucleic acid sequence complementary to (a); and
- (c) a functional fragment of (a) or (b).

6. The recombinant vector according to claim 5, wherein said vector further comprises a 5' AAV-1 ITR.

7. The recombinant vector according to any of claims 3-6, wherein said vector further comprises AAV-1 capsid proteins having the sequence of SEQ ID NO: 13, 15 or 17 or functional fragments thereof.

8. The recombinant vector according to any of claims 3-6, wherein said vector further comprises adenovirus sequences.

9. A recombinant vector comprising an AAV-1 P5 promoter having the sequence of nt 236 to 299 of SEQ ID NO: 1 or a functional fragment thereof.

10. A nucleic acid molecule encoding AAV-1 helper functions, said molecule comprising an AAV rep coding region and an AAV cap coding region, wherein said cap coding region comprises at least one member is selected from the group consisting of:

- (a) vp1, nt 2223 to 4431 of SEQ ID NO: 1;
- (b) vp2, nt 2634 to 4432 of SEQ ID NO: 1; and
- (c) vp3, nt 2829 to 4432 of SEQ ID NO: 1.

11. A nucleic acid molecule encoding AAV-1 helper functions, said molecule comprising an AAV rep coding region and an AAV cap coding region, wherein said rep coding region comprises an AAV-1 rep coding region comprising at least one member selected from the group consisting of:

- (a) rep 78, nt 335 to 2304 of SEQ ID NO: 1;
- (b) rep 68, nt 335 to 2272 of SEQ ID NO: 1 or the cDNA corresponding thereto;
- (c) rep 52, nt 1007 to 2304 of SEQ ID NO: 1; and
- (d) rep 40, nt 1007 to 2272 of SEQ ID NO: 1 or the cDNA corresponding thereto.

12. A host cell transduced with a recombinant viral vector according to any of claims 3-6.

13. A host cell transduced with a nucleic acid molecule according to any of claims 1, 2, 10 or 11.

14. A host cell stably transduced with an AAV-1 P5 promoter having the sequence of nt 236 to 299 of SEQ ID NO: 1.

15. A pharmaceutical composition comprising a carrier and a virus comprising the vector according to any of claims 3-6.

16. A pharmaceutical composition comprising a carrier and a virus comprising the vector according to claim 7.

17. A pharmaceutical composition comprising a carrier and a virus comprising the vector according to claim 8.

18. A method for AAV-mediated delivery of a transgene comprising the step of delivering to a host cell an AAV virion which comprises:

(a) a capsid comprising at least one capsid protein encoded by an AAV-1 cap gene; and

(b) a DNA molecule comprising a transgene under the control of regulatory sequences directing its expression.

19. A method for AAV-mediated delivery of a transgene to a host comprising the steps of:

(a) assaying a sample from the host to determine the presence of neutralizing antibodies specific against any serotype of AAV; and

(b) delivering to the host an AAV virion which comprises:

(i) a capsid comprising at least one capsid protein encoded by a cap gene of an AAV serotype against which the host has no antibodies as determined in step (a); and

(ii) a DNA molecule comprising a transgene under the control of regulatory sequences directing its expression.

20. The method according to claim 19, comprising the additional step of repeating steps (a) and (b).

21. Use of an AAV virion which comprises a capsid comprising (a) at least one capsid protein encoded by a cap gene of an AAV serotype against which the host has antibodies, and (b) a DNA molecule comprising a transgene operably linked to regulatory sequences directing its expression,

in the preparation of a medicament for delivery of a transgene to a host, wherein said host has no preexisting neutralizing antibodies against the AAV serotype of said cap gene.

22. A method for delivery of a transgene comprising the step of delivering to a host cell a recombinant virus comprising a recombinant vector according to any of claims 3-8.

23. A method for producing a selected gene product comprising the steps of transfecting a mammalian cell with the molecule according to claim 1 or a functional fragment thereof and culturing said cell under conditions suitable to express said gene product.

FIG 1B

AAV-1 CCGACAGGTACCAAAACAAATGTTCTGTCACGCGGCACTGCTCAGATGCTGTTCCCTGCAAGCATGCGAGAGAATGAATCAGAATTTCAACATTGCTTCACGCACGGGACGAGAG 2036
AAV-2 .A.T.AA.GACA.CA.T.ACA. 2019
AAV-6A. 2021

AAV-1 ACTGTTCAAGTCTTCCCCGCTGTCAGAATCTCAACGGTC---GTCAGAAAGAGGAGCTATCGGAACTCTGTGCCATTATCATCTGCTGGGGCGGGCTCCCGAGATTGCTTCT 2153
AAV-2T.C.GTC.A.G.CTA.A.AAA.TG.C.A 2133
AAV-6A. 2138

Rep78 stop VP1 Rep68 stop
AAV-1 CCGCTGCGATCTGCTCAACGTGACCTGGATGACTGTGTTCTGAGCAATAAATGACTTAAACAGGTATGCTGCGGATGTTATCTTCCAGATTGGCTCGAGGACAACCTCTCTGAG 2273
AAV-2T.TT.CA.T.T.CT.A 2253
AAV-6T.AC.G 2258

AAV-1 GGCATTGCGGAGTGTGGGACTTCAAACTGGAGCCCCGAAAGCCCAAGCCAAACAGCAAAAGCAGGACGACGGCGGGCTCTGGTCTTCTGGCTACAAGTACCTGGACCCCTCAAC 2393
AAV-2AA.CC.A.GC.GCA.G.T.G. 2373
AAV-6A.G.C.G.C. 2378

AAV-1 GGACTCCACAAGGGCGAGCCCTCAACGCGCGGAGCGCAGCGGCGCTGAGCAAGCAAGCCCTACGACGAGCTCAAAGCGGGTGACAATCCGTACTGCGGTATAACCAAGCGGCGAC 2513
AAV-2A.G.A.C.A.G.G.C.CAA.C. 2493
AAV-6T.A.T.GCG.T. 2498

AAV-1 GCGGATTTCAAGAGCGCTCTGCAAGAGATAAGTCTTTTGGGGCAACCTCGGGGAGCAGCTCTTCCAGCCCAAGAGCGGGTCTCGAACCTCTCGGTCTGGTTCAGGAGGGCGCTAAG 2633
AAV-2G.C.TA.A.G.A.T.G.C.CCT.T. 2613
AAV-6C.T.G.A.T.T.T. 2618

VP2
AAV-1 ACGGCTCTCGAAGAAAGCTCCGGTAGAGCTGCGCACAGAGCCGACTCTCTCGGCGATCGGCAAGAGCCGAGCCGAGCCCGCTAAAGAGAGACTCAATTTGGTCAAGTGGC 2753
AAV-2G.A.CA.G.T.T.A.G.T.A.G. 2733
AAV-6T.G.G.ACAA.T. 2738

VP3
AAV-1 GACTCAGAGTCACTCCCGATCCACAACCTCTCGGAGAACCTCCAGCAACCCCGCTGCTGCGGACCTACTACAATGGCTTCAGGCGGTGGCGACCAATGGCAGACAATAACGAAGGC 2873
AAV-2G.C.G.G.G.A.G.A.G.A.G. 2853
AAV-6T.G.C.A.G.A.G. 2858

AAV-1 GCGGACCGAGTGGTAATGCTCAGAAATGGCAATTCGATTCACATGGCTGGGCGACAGATCATACCAACGACCCGACCTGGGCTTGGCCACCTACAATAACCACTCTAC 2993
AAV-2T.C.A.A.A.C.C.C.C. 2973
AAV-6A.A.T.C. 2978

AAV-1 AAGCAATCTCCAGTCTTCAACGGGGGCAAGCAAGCAACCACTACTTCGGGTACAGCAACCCCTGGGGTATTTTGATTTCACAGATTCCACTGCCATTTTCAACGAGTACTGG 3113
AAV-2A.T.CCA.A.TCG.T.T.T.C. 3090
AAV-6A.A.T.C. 3098

AAV-1 CAGGACTCATCAACAATTTGGGATTCGGGCGCAAGAGACTCACTTCAACTCTTCACTCAAGTCAAGGAGGTCAAGCAATGATGGGCTCAGAACCATCTCTAATAACCTT 3233
AAV-2AA.C.A.G.T.T.A.CA.C.T.C. 3210
AAV-6A.G. 3218

AAV-1 ACCAGACGGTTCAAGTCTTCTGGGACTCGGAGTACCAGCTTCCGTAGCTCTGGCTCTGGCCACGAGGCTCCCTCCCTGCTCCGGCGGAGCGTGTTCATGATTCGGCAATACGGC 3353
AAV-2G.G.TA.C.G.G.G.A.A.G.A. 3330
AAV-6T.G. 3338

AAV-1 TACCTGACCTCAACAATGGCAGCCAGCGGTGAGCTTCTCTTTTCTGCTGGAATATTTCTCTCTCAGATGCTGAGAACGGGCAACAACTTTACTTTCAGTACACTTTGAG 3473
AAV-2C.C.G.T.G.A.C.T.A.G.C.T.C. 3450
AAV-6A.G.A.G.A.G.T.T.C. 3458

AAV-1 GAAGTCCCTTTCCACAGAGCTACCGGCAAGCCAGGCTGGAGCGGCTGATGAATCTCTCATCGACCAATACCTGTATTACTGAACAGAACTCAAAATCAGTCCGGAAGTCCCAA 3593
AAV-2C.T.T.T.T.G.T.G.AA.C.CAAGT.CCA.ACG 3570
AAV-6C.G. 3578

AAV-1 AACAAGGACTGCTGTTTACCGTGGTCTCCAGCTGCGATGTCTGTTCAAGCCAAAAGTGGCTACCTGGACCTGTTATCGGAGCAGCGGCTTCTTAAACAAAACAGACAACAC 3713
AAV-2C.G.T.T.T.T.T.T.C.C.A.CA.G.T. 3690
AAV-6G. 3698

AAV-1 AAGCAATTTTACCTGGAGTGGTCTTCAAAATATAACCTCAATGGGCGTGAATCCATCATCAACCTGGCACTGCTATGGCTTCAACAAGAGAGAGCAAGTCTTTCCCATG 3833
AAV-2TG.A.A.A.C.CC.CA.C.TC.G.G.GC.C.AAGC.G. 3810
AAV-6C.T.T.A. 3818

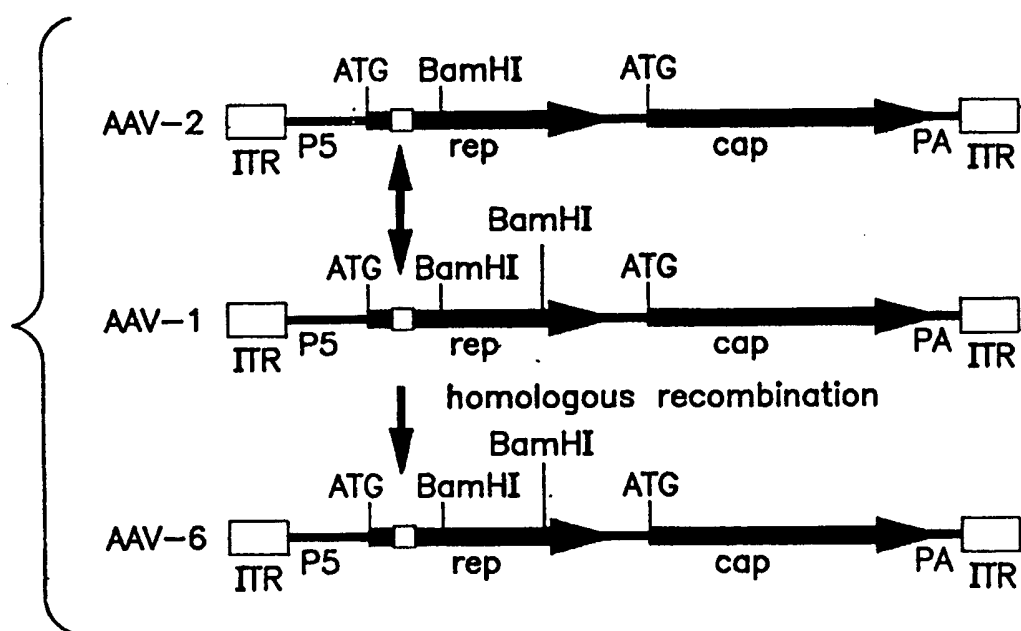


FIG. 3A

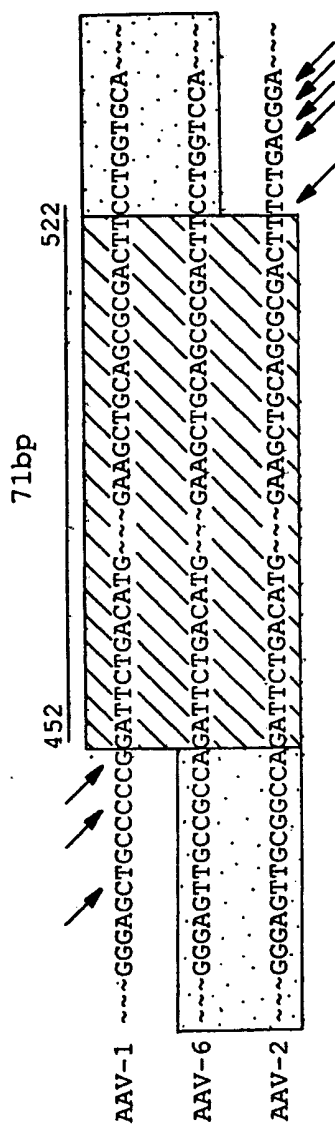


FIG. 3B

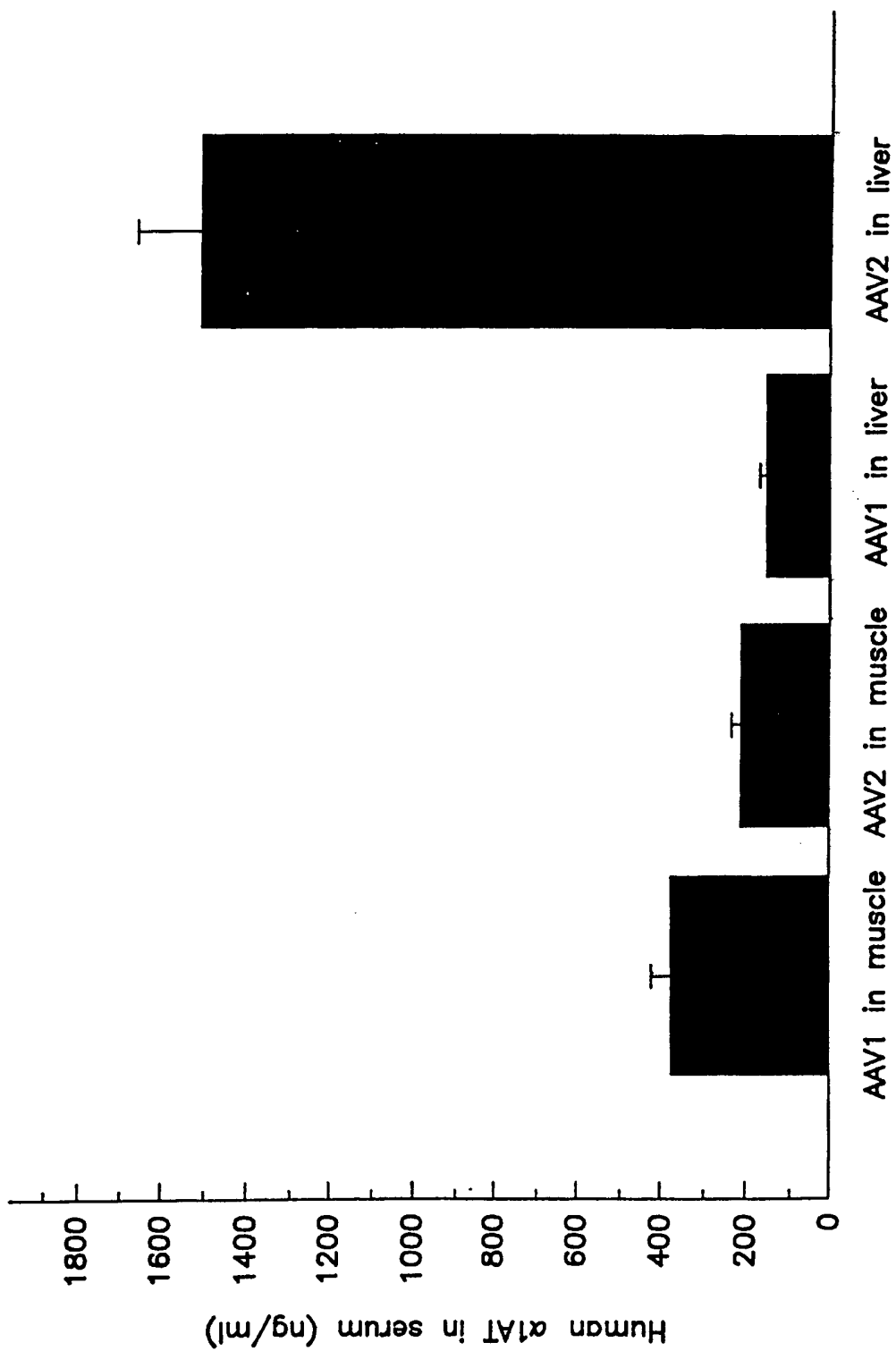


FIG. 4A

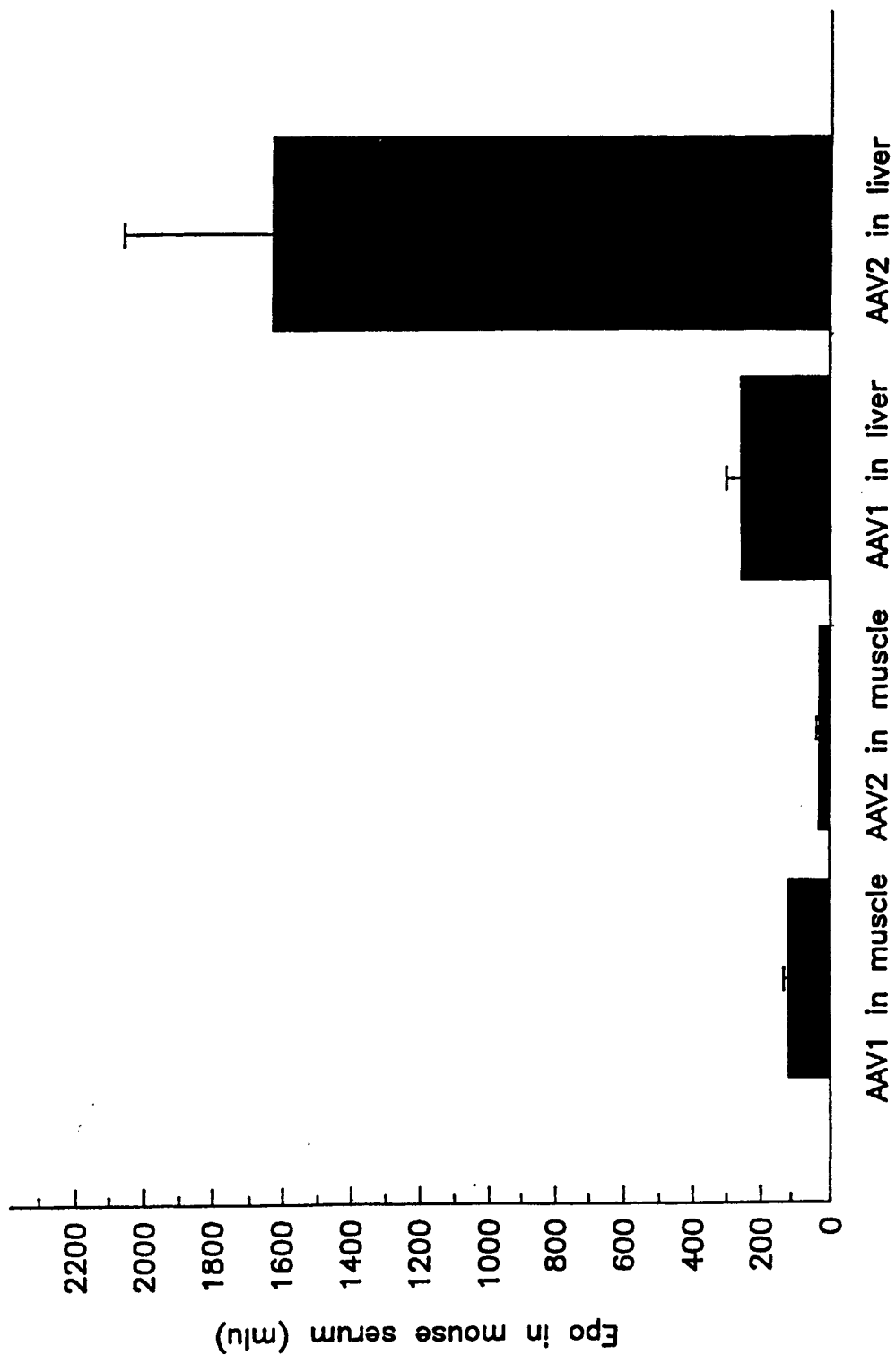


FIG. 4B

FIG. 5A

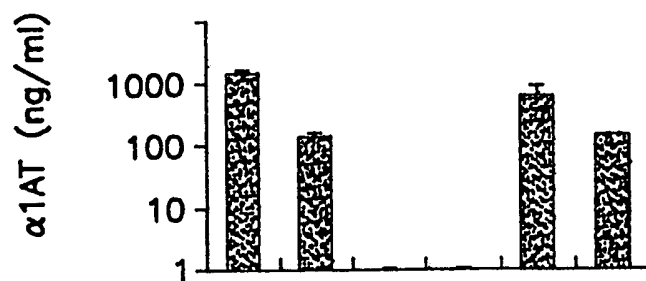


FIG. 5B

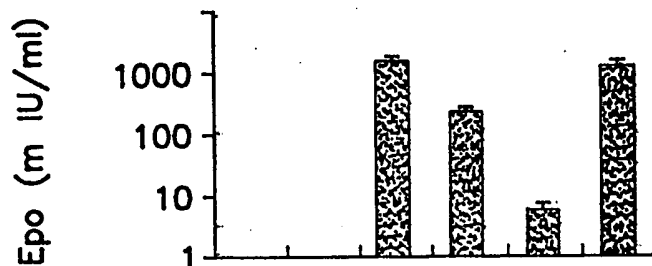


FIG. 5C

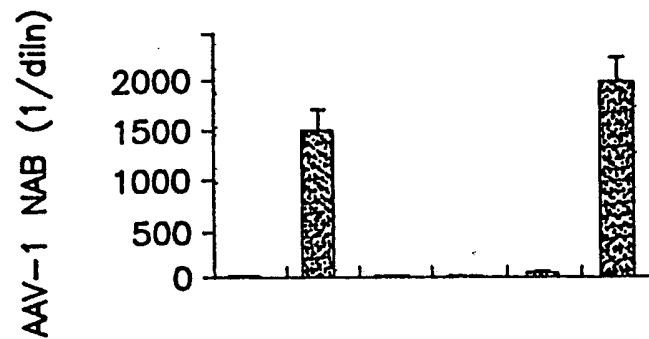
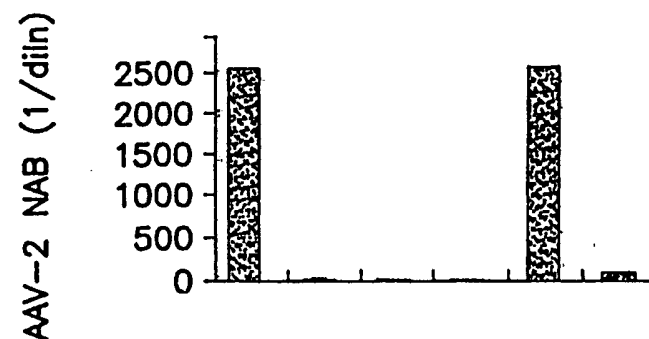


FIG. 5D



Group	1	2	3	4	5	6
Vector1- α 1AT	AAV2	AAV1	PBS	PBS	AAV2	AAV1
Vector2-EPO	AAV2	AAV1	AAV2	AAV1	AAV1	AAV2

FIG. 6A

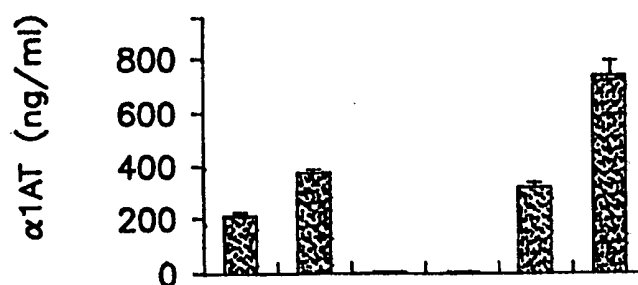


FIG. 6B

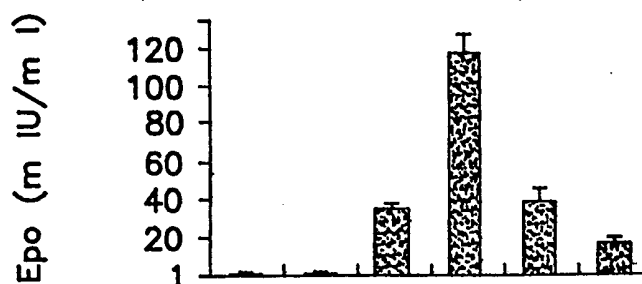


FIG. 6C

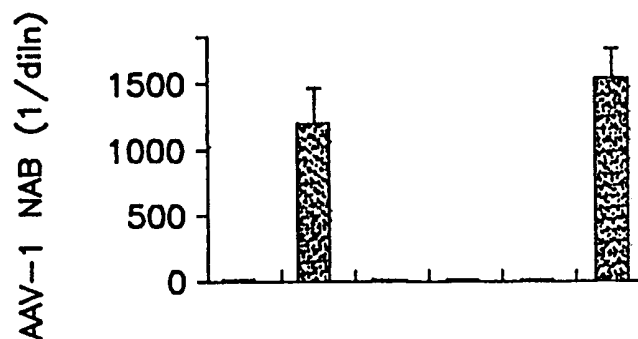
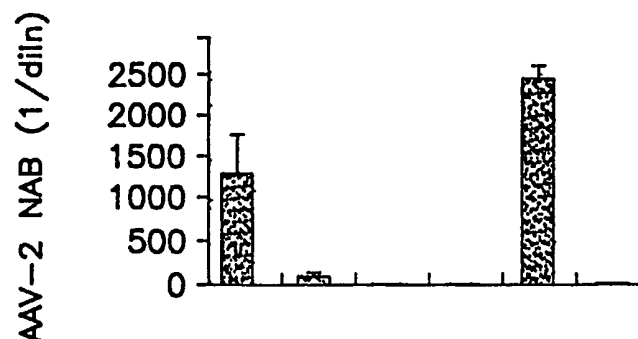


FIG. 6D



Group	1	2	3	4	5	6
Vector1- α 1AT	AAV2	AAV1	PBS	PBS	AAV2	AAV1
Vector2-EPO	AAV2	AAV1	AAV2	AAV1	AAV1	AAV2

SEQUENCE LISTING

<110> Wilson, James M.

Xiao, Weidong

The Trustees of the University of Pennsylvania

<120> Adeno-Associated Virus Serotype I Nucleic Acid
Sequences, Vectors and Host Cells Containing Same

<130> GNVPN.031PCT

<140>

<141>

<150> 60/107,114

<151> 1998-11-05

<160> 20

<170> PatentIn Ver. 2.0

<210> 1

<211> 4718

<212> DNA

<213> AAV-1

<220>

<221> CDS

<222> (335)..(2206)

<220>

<221> CDS

<222> (2223)..(4430)

<400> 1

ttgccactc cctctctgcg cgctcgctcg ctcggtgggg cctgcggacc aaaggtccgc 60

agacggcaga gctctgctct gccggcccca ccgagcgagc gagcgcgagc agagggagtg 120

ggcaactcca tctactagggg taatcgcgaa gcgcctccca cgctgccgcg tcagcgctga 180

cgtaaattac gtcataagggg agtggctctg tattagctgt cacgtgagtg cttttgcgac 240

attttgcgac accacgtggc catttagggt atatatggcc gagtgagcga gcaggatctc 300

cattttgacc gcgaaatttg aacgagcagc agcc atg ccg ggc ttc tac gag atc 355

Met Pro Gly Phe Tyr Glu Ile

1

5

gtg atc aag gtg ccg agc gac ctg gac gag cac ctg ccg ggc att tct	403
Val Ile Lys Val Pro Ser Asp Leu Asp Glu His Leu Pro Gly Ile Ser	
10 15 20	
gac tcg ttt gtg agc tgg gtg gcc gag aag gaa tgg gag ctg ccc ccg	451
Asp Ser Phe Val Ser Trp Val Ala Glu Lys Glu Trp Glu Leu Pro Pro	
25 30 35	
gat tct gac atg gat ctg aat ctg att gag cag gca ccc ctg acc gtg	499
Asp Ser Asp Met Asp Leu Asn Leu Ile Glu Gln Ala Pro Leu Thr Val	
40 45 50 55	
gcc gag aag ctg cag cgc gac ttc ctg gtc caa tgg cgc cgc gtg agt	547
Ala Glu Lys Leu Gln Arg Asp Phe Leu Val Gln Trp Arg Arg Val Ser	
60 65 70	
aag gcc ccg gag gcc ctc ttc ttt gtt cag ttc gag aag ggc gag tcc	595
Lys Ala Pro Glu Ala Leu Phe Phe Val Gln Phe Glu Lys Gly Glu Ser	
75 80 85	
tac ttc cac ctc cat att ctg gtg gag acc acg ggg gtc aaa tcc atg	643
Tyr Phe His Leu His Ile Leu Val Glu Thr Thr Gly Val Lys Ser Met	
90 95 100	
gtg ctg ggc cgc ttc ctg agt cag att agg gac aag ctg gtg cag acc	691
Val Leu Gly Arg Phe Leu Ser Gln Ile Arg Asp Lys Leu Val Gln Thr	
105 110 115	
atc tac cgc ggg atc gag ccg acc ctg ccc aac tgg ttc gcg gtg acc	739
Ile Tyr Arg Gly Ile Glu Pro Thr Leu Pro Asn Trp Phe Ala Val Thr	
120 125 130 135	
aag acg cgt aat ggc gcc gga ggg ggg aac aag gtg gtg gac gag tgc	787
Lys Thr Arg Asn Gly Ala Gly Gly Gly Asn Lys Val Val Asp Glu Cys	
140 145 150	
tac atc ccc aac tac ctc ctg ccc aag act cag ccc gag ctg cag tgg	835
Tyr Ile Pro Asn Tyr Leu Leu Pro Lys Thr Gln Pro Glu Leu Gln Trp	
155 160 165	
gcg tgg act aac atg gag gag tat ata agc gcc tgt ttg aac ctg gcc	883
Ala Trp Thr Asn Met Glu Glu Tyr Ile Ser Ala Cys Leu Asn Leu Ala	
170 175 180	
gag cgc aaa cgg ctc gtg gcg cag cac ctg acc cac gtc agc cag acc	931
Glu Arg Lys Arg Leu Val Ala Gln His Leu Thr His Val Ser Gln Thr	
185 190 195	

cag gag cag aac aag gag aat ctg aac ccc aat tct gac gcg cct gtc	979
Gln Glu Gln Asn Lys Glu Asn Leu Asn Pro Asn Ser Asp Ala Pro Val	
200 205 210 215	
atc cgg tca aaa acc tcc gcg cgc tac atg gag ctg gtc ggg tgg ctg	1027
Ile Arg Ser Lys Thr Ser Ala Arg Tyr Met Glu Leu Val Gly Trp Leu	
220 225 230	
gtg gac cgg ggc atc acc tcc gag aag cag tgg atc cag gag gac cag	1075
Val Asp Arg Gly Ile Thr Ser Glu Lys Gln Trp Ile Gln Glu Asp Gln	
235 240 245	
gcc tcg tac atc tcc ttc aac gcc gct tcc aac tcg cgg tcc cag atc	1123
Ala Ser Tyr Ile Ser Phe Asn Ala Ala Ser Asn Ser Arg Ser Gln Ile	
250 255 260	
aag gcc gct ctg gac aat gcc ggc aag atc atg gcg ctg acc aaa tcc	1171
Lys Ala Ala Leu Asp Asn Ala Gly Lys Ile Met Ala Leu Thr Lys Ser	
265 270 275	
gcg ccc gac tac ctg gta ggc ccc gct ccg ccc gcg gac att aaa acc	1219
Ala Pro Asp Tyr Leu Val Gly Pro Ala Pro Pro Ala Asp Ile Lys Thr	
280 285 290 295	
aac cgc atc tac cgc atc ctg gag ctg aac ggc tac gaa cct gcc tac	1267
Asn Arg Ile Tyr Arg Ile Leu Glu Leu Asn Gly Tyr Glu Pro Ala Tyr	
300 305 310	
gcc ggc tcc gtc ttt ctc ggc tgg gcc cag aaa agg ttc ggg aag cgc	1315
Ala Gly Ser Val Phe Leu Gly Trp Ala Gln Lys Arg Phe Gly Lys Arg	
315 320 325	
aac acc atc tgg ctg ttt ggg ccg gcc acc acg ggc aag acc aac atc	1363
Asn Thr Ile Trp Leu Phe Gly Pro Ala Thr Thr Gly Lys Thr Asn Ile	
330 335 340	
gcg gaa gcc atc gcc cac gcc gtg ccc ttc tac ggc tgc gtc aac tgg	1411
Ala Glu Ala Ile Ala His Ala Val Pro Phe Tyr Gly Cys Val Asn Trp	
345 350 355	
acc aat gag aac ttt ccc ttc aat gat tgc gtc gac aag atg gtg atc	1459
Thr Asn Glu Asn Phe Pro Phe Asn Asp Cys Val Asp Lys Met Val Ile	
360 365 370 375	
tgg tgg gag gag ggc aag atg acg gcc aag gtc gtg gag tcc gcc aag	1507
Trp Trp Glu Glu Gly Lys Met Thr Ala Lys Val Val Glu Ser Ala Lys	
380 385 390	

```

gcc att ctc ggc ggc agc aag gtg cgc gtg gac caa aag tgc aag tcg 1555
Ala Ile Leu Gly Gly Ser Lys Val Arg Val Asp Gln Lys Cys Lys Ser
      395                      400                      405

tcc gcc cag atc gac ccc acc ccc gtg atc gtc acc tcc aac acc aac 1603
Ser Ala Gln Ile Asp Pro Thr Pro Val Ile Val Thr Ser Asn Thr Asn
      410                      415                      420

atg tgc gcc gtg att gac ggg aac agc acc acc ttc gag cac cag cag 1651
Met Cys Ala Val Ile Asp Gly Asn Ser Thr Thr Phe Glu His Gln Gln
      425                      430                      435

ccg ttg cag gac cgg atg ttc aaa ttt gaa ctc acc cgc cgt ctg gag 1699
Pro Leu Gln Asp Arg Met Phe Lys Phe Glu Leu Thr Arg Arg Leu Glu
      440                      445                      450                      455

cat gac ttt ggc aag gtg aca aag cag gaa gtc aaa gag ttc ttc cgc 1747
His Asp Phe Gly Lys Val Thr Lys Gln Glu Val Lys Glu Phe Phe Arg
      460                      465                      470

tgg gcg cag gat cac gtg acc gag gtg gcg cat gag ttc tac gtc aga 1795
Trp Ala Gln Asp His Val Thr Glu Val Ala His Glu Phe Tyr Val Arg
      475                      480                      485

aag ggt gga gcc aac aaa aga ccc gcc ccc gat gac gcg gat aaa agc 1843
Lys Gly Gly Ala Asn Lys Arg Pro Ala Pro Asp Asp Ala Asp Lys Ser
      490                      495                      500

gag ccc aag cgg gcc tgc ccc tca gtc gcg gat cca tcg acg tca gac 1891
Glu Pro Lys Arg Ala Cys Pro Ser Val Ala Asp Pro Ser Thr Ser Asp
      505                      510                      515

gcg gaa gga gct ccg gtg gac ttt gcc gac agg tac caa aac aaa tgt 1939
Ala Glu Gly Ala Pro Val Asp Phe Ala Asp Arg Tyr Gln Asn Lys Cys
      520                      525                      530                      535

tct cgt cac gcg ggc atg ctt cag atg ctg ttt ccc tgc aag aca tgc 1987
Ser Arg His Ala Gly Met Leu Gln Met Leu Phe Pro Cys Lys Thr Cys
      540                      545                      550

gag aga atg aat cag aat ttc aac att tgc ttc acg cac ggg acg aga 2035
Glu Arg Met Asn Gln Asn Phe Asn Ile Cys Phe Thr His Gly Thr Arg
      555                      560                      565

gac tgt tca gag tgc ttc ccc gcc gtg tca gaa tct caa ccg gtc gtc 2083
Asp Cys Ser Glu Cys Phe Pro Gly Val Ser Glu Ser Gln Pro Val Val
      570                      575                      580

```

aga aag agg acg tat cgg aaa ctc tgt gcc att cat cat ctg ctg ggg 2131
 Arg Lys Arg Thr Tyr Arg Lys Leu Cys Ala Ile His His Leu Leu Gly
 585 590 595

cgg gct ccc gag att gct tgc tgc gcc tgc gat ctg gtc aac gtg gac 2179
 Arg Ala Pro Glu Ile Ala Cys Ser Ala Cys Asp Leu Val Asn Val Asp
 600 605 610 615

ctg gat gac tgt gtt tct gag caa taa atgacttaaa ccaggt atg gct gcc 2231
 Leu Asp Asp Cys Val Ser Glu Gln Met Ala Ala
 620 625

gat ggt tat ctt cca gat tgg ctc gag gac aac ctc tct gag ggc att 2279
 Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser Glu Gly Ile
 630 635 640

cgc gag tgg tgg gac ttg aaa cct gga gcc ccg aag ccc aaa gcc aac 2327
 Arg Glu Trp Trp Asp Leu Lys Pro Gly Ala Pro Lys Pro Lys Ala Asn
 645 650 655

cag caa aag cag gac gac ggc cgg ggt ctg gtg ctt cct ggc tac aag 2375
 Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro Gly Tyr Lys
 660 665 670 675

tac ctc gga ccc ttc aac gga ctc gac aag ggg gag ccc gtc aac gcg 2423
 Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro Val Asn Ala
 680 685 690

gcg gac gca gcg gcc ctc gag cac gac aag gcc tac gac cag cag ctc 2471
 Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp Gln Gln Leu
 695 700 705

aaa gcg ggt gac aat ccg tac ctg cgg tat aac cac gcc gac gcc gag 2519
 Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala Asp Ala Glu
 710 715 720

ttt cag gag cgt ctg caa gaa gat acg tct ttt ggg ggc aac ctc ggg 2567
 Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly Asn Leu Gly
 725 730 735

cga gca gtc ttc cag gcc aag aag cgg gtt ctc gaa cct ctc ggt ctg 2615
 Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro Leu Gly Leu
 740 745 750 755

gtt gag gaa ggc gct aag acg gct cct gga aag aaa cgt ccg gta gag 2663
 Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg Pro Val Glu
 760 765 770

cag tcg cca caa gag cca gac tcc tcc tcg ggc atc ggc aag aca ggc	2711
Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly Lys Thr Gly	
775 780 785	
cag cag ccc gct aaa aag aga ctc aat ttt ggt cag act ggc gac tca	2759
Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr Gly Asp Ser	
790 795 800	
gag tca gtc ccc gat cca caa cct ctc gga gaa cct cca gca acc ccc	2807
Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro Ala Thr Pro	
805 810 815	
gct gct gtg gga cct act aca atg gct tca ggc ggt ggc gca cca atg	2855
Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly Ala Pro Met	
820 825 830 835	
gca gac aat aac gaa ggc gcc gac gga gtg ggt aat gcc tca gga aat	2903
Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala Ser Gly Asn	
840 845 850	
tgg cat tgc gat tcc aca tgg ctg ggc gac aga gtc atc acc acc agc	2951
Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile Thr Thr Ser	
855 860 865	
acc cgc acc tgg gcc ttg ccc acc tac aat aac cac ctc tac aag caa	2999
Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu Tyr Lys Gln	
870 875 880	
atc tcc agt gct tca acg ggg gcc agc aac gac aac cac tac ttc ggc	3047
Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His Tyr Phe Gly	
885 890 895	
tac agc acc ccc tgg ggg tat ttt gat ttc aac aga ttc cac tgc cac	3095
Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe His Cys His	
900 905 910 915	
ttt tca cca cgt gac tgg cag cga ctc atc aac aac aat tgg gga ttc	3143
Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn Trp Gly Phe	
920 925 930	
cgg ccc aag aga ctc aac ttc aaa ctc ttc aac atc caa gtc aag gag	3191
Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln Val Lys Glu	
935 940 945	
gtc acg acg aat gat ggc gtc aca acc atc gct aat aac ctt acc agc	3239
Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn Leu Thr Ser	
950 955 960	

acg gtt caa gtc ttc tcg gac tcg gag tac cag ctt ccg tac gtc ctc 3287
 Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro Tyr Val Leu
 965 970 975

ggc tct gcg cac cag ggc tgc ctc cct ccg ttc ccg gcg gac gtg ttc 3335
 Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala Asp Val Phe
 980 985 990 995

atg att ccg caa tac ggc tac ctg acg ctc aac aat ggc agc caa gcc 3383
 Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly Ser Gln Ala
 1000 1005 1010

gtg gga cgt tca tcc ttt tac tgc ctg gaa tat ttc cct tct cag atg 3431
 Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro Ser Gln Met
 1015 1020 1025

ctg aga acg ggc aac aac ttt acc ttc agc tac acc ttt gag gaa gtg 3479
 Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe Glu Glu Val
 1030 1035 1040

cct ttc cac agc agc tac gcg cac agc cag agc ctg gac cgg ctg atg 3527
 Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met
 1045 1050 1055

aat cct ctc atc gac caa tac ctg tat tac ctg aac aga act caa aat 3575
 Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Asn Arg Thr Gln Asn
 1060 1065 1070 1075

cag tcc gga agt gcc caa aac aag gac ttg ctg ttt agc cgt ggg tct 3623
 Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser Arg Gly Ser
 1080 1085 1090

cca gct ggc atg tct gtt cag ccc aaa aac tgg cta cct gga ccc tgt 3671
 Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro Gly Pro Cys
 1095 1100 1105

tat cgg cag cag cgc gtt tct aaa aca aaa aca gac aac aac aac agc 3719
 Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn Asn Asn Ser
 1110 1115 1120

aat ttt acc tgg act ggt gct tca aaa tat aac ctc aat ggg cgt gaa 3767
 Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn Gly Arg Glu
 1125 1130 1135

tcc atc atc aac cct ggc act gct atg gcc tca cac aaa gac gac gaa 3815
 Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys Asp Asp Glu
 1140 1145 1150 1155

gac aag ttc ttt ccc atg agc ggt gtc atg att ttt gga aaa gag agc 3863
 Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe Gly Lys Glu Ser
 1160 1165 1170

gcc gga gct tca aac act gca ttg gac aat gtc atg att aca gac gaa 3911
 Ala Gly Ala Ser Asn Thr Ala Leu Asp Asn Val Met Ile Thr Asp Glu
 1175 1180 1185

gag gaa att aaa gcc act aac cct gtg gcc acc gaa aga ttt ggg acc 3959
 Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg Phe Gly Thr
 1190 1195 1200

gtg gca gtc aat ttc cag agc agc agc aca gac cct gcg acc gga gat 4007
 Val Ala Val Asn Phe Gln Ser Ser Ser Thr Asp Pro Ala Thr Gly Asp
 1205 1210 1215

gtg cat gct atg gga gca tta cct ggc atg gtg tgg caa gat aga gac 4055
 Val His Ala Met Gly Ala Leu Pro Gly Met Val Trp Gln Asp Arg Asp
 1220 1225 1230 1235

gtg tac ctg cag ggt ccc att tgg gcc aaa att cct cac aca gat gga 4103
 Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly
 1240 1245 1250

cac ttt cac ccg tct cct ctt atg ggc ggc ttt gga ctc aag aac ccg 4151
 His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu Lys Asn Pro
 1255 1260 1265

cct cct cag atc ctc atc aaa aac acg cct gtt cct gcg aat cct ccg 4199
 Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala Asn Pro Pro
 1270 1275 1280

gcg gag ttt tca gct aca aag ttt gct tca ttc atc acc caa tac tcc 4247
 Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr Gln Tyr Ser
 1285 1290 1295

aca gga caa gtg agt gtg gaa att gaa tgg gag ctg cag aaa gaa aac 4295
 Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln Lys Glu Asn
 1300 1305 1310 1315

agc aag cgc tgg aat ccc gaa gtg cag tac aca tcc aat tat gca aaa 4343
 Ser Lys Arg Trp Asn Pro Glu Val Gln Tyr Thr Ser Asn Tyr Ala Lys
 1320 1325 1330

tct gcc aac gtt gat ttt act gtg gac aac aat gga ctt tat act gag 4391
 Ser Ala Asn Val Asp Phe Thr Val Asp Asn Asn Gly Leu Tyr Thr Glu
 1335 1340 1345

cct cgc ccc att ggc acc cgt tac ctt acc cgt ccc ctg taattacgtg 4440
 Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Pro Leu
 1350 1355 1360

ttaatcaata aaccggttga ttcgtttcag ttgaactttg gtctctctgtc cttcttatct 4500
 tatcgggttac catggttata gcttacacat taactgcttg gttgcgcttc gcgataaaaag 4560
 acttacgtca tcgggttacc cctagtgatg gagttgccca ctccctctct gcgcgctcgc 4620
 tcgctcggtg gggcctgcgg accaaaggtc cgcagacggc agagctctgc tctgccggcc 4680
 ccaccgagcg agcgagcgcg cagagagggg .gtggggcaa 4718

<210> 2
 <211> 623
 <212> PRT
 <213> AAV-1

<400> 2
 Met Pro Gly Phe Tyr Glu Ile Val Ile Lys Val Pro Ser Asp Leu Asp
 1 5 10 15

Glu His Leu Pro Gly Ile Ser Asp Ser Phe Val Ser Trp Val Ala Glu
 20 25 30

Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile
 35 40 45

Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
 50 55 60

Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
 65 70 75 80

Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu
 85 90 95

Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
 100 105 110

Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu
 115 120 125

Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly
 130 135 140

Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys
 145 150 155 160

Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile
 165 170 175

Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His
 180 185 190

Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn
 195 200 205

Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr
 210 215 220

Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
 225 230 235 240

Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 245 250 255

Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
 260 265 270

Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
 275 280 285

Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
 290 295 300

Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
 305 310 315 320

Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
 325 330 335

Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
 340 345 350

Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
 355 360 365

Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
 370 375 380

Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
 385 390 395 400

Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
 405 410 415

Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
 420 425 430

Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
 435 440 445

Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
 450 455 460

Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
 465 470 475 480

Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
 485 490 495

Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
 500 505 510

Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
 515 520 525

Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met
 530 535 540

Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile
 545 550 555 560

Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val
 565 570 575

Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys
 580 585 590

Ala Ile His His Leu Leu Gly Arg Ala Pro Glu Ile Ala Cys Ser Ala
 595 600 605

Cys Asp Leu Val Asn Val Asp Leu Asp Asp Cys Val Ser Glu Gln
 610 615 620

<210> 3

<211> 736

<212> PRT

<213> AAV-1

<400> 3

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
 1 5 10 15

Glu Gly Ile Arg Glu Trp Trp Asp Leu Lys Pro Gly Ala Pro Lys Pro
 20 25 30

Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro
 35 40 45

Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
 50 55 60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
 65 70 75 80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
 85 90 95

Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
 100 105 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
 115 120 125

Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
 130 135 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly
 145 150 155 160

Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
 165 170 175

Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro
 180 185 190

Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
 195 200 205

Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala
 210 215 220

Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile
 225 230 235 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu

	245		250		255
Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His					
	260		265		270
Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe					
	275		280		285
His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn					
	290		295		300
Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln					
	305		310		315 320
Val Lys Glu Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn					
	325		330		335
Leu Thr Ser Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro					
	340		345		350
Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala					
	355		360		365
Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly					
	370		375		380
Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro					
	385		390		395 400
Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe					
	405		410		415
Glu Glu Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp					
	420		425		430
Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Asn Arg					
	435		440		445
Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser					
	450		455		460
Arg Gly Ser Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro					
	465		470		475 480
Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn					
	485		490		495
Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn					

500	505	510
Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys		
515	520	525
Asp Asp Glu Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe Gly		
530	535	540
Lys Glu Ser Ala Gly Ala Ser Asn Thr Ala Leu Asp Asn Val Met Ile		
545	550	555
Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg		
565	570	575
Phe Gly Thr Val Ala Val Asn Phe Gln Ser Ser Ser Thr Asp Pro Ala		
580	585	590
Thr Gly Asp Val His Ala Met Gly Ala Leu Pro Gly Met Val Trp Gln		
595	600	605
Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His		
610	615	620
Thr Asp Gly His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu		
625	630	635
Lys Asn Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala		
645	650	655
Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr		
660	665	670
Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln		
675	680	685
Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Val Gln Tyr Thr Ser Asn		
690	695	700
Tyr Ala Lys Ser Ala Asn Val Asp Phe Thr Val Asp Asn Asn Gly Leu		
705	710	715
Tyr Thr Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Pro Leu		
725	730	735

<210> 4

<211> 1872

<212> DNA

<213> AAV-1

<220>

<221> CDS

<222> (1)..(1869)

<400> 4

atg ccg ggc ttc tac gag atc gtg atc aag gtg ccg agc gac ctg gac	48
Met Pro Gly Phe Tyr Glu Ile Val Ile Lys Val Pro Ser Asp Leu Asp	
1 5 10 15	
 gag cac ctg ccg ggc att tct gac tcg ttt gtg agc tgg gtg gcc gag	96
Glu His Leu Pro Gly Ile Ser Asp Ser Phe Val Ser Trp Val Ala Glu	
20 25 30	
 aag gaa tgg gag ctg ccc ccg gat tct gac atg gat ctg aat ctg att	144
Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile	
35 40 45	
 gag cag gca ccc ctg acc gtg gcc gag aag ctg cag cgc gac ttc ctg	192
Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu	
50 55 60	
 gtc caa tgg cgc cgc gtg agt aag gcc ccg gag gcc ctc ttc ttt gtt	240
Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val	
65 70 75 80	
 cag ttc gag aag ggc gag tcc tac ttc cac ctc cat att ctg gtg gag	288
Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu	
85 90 95	
 acc acg ggg gtc aaa tcc atg gtg ctg ggc cgc ttc ctg agt cag att	336
Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile	
100 105 110	
 agg gac aag ctg gtg cag acc atc tac cgc ggg atc gag ccg acc ctg	384
Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu	
115 120 125	
 ccc aac tgg ttc gcg gtg acc aag acg cgt aat ggc gcc gga ggg ggg	432
Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly	
130 135 140	
 aac aag gtg gtg gac gag tgc tac atc ccc aac tac ctc ctg ccc aag	480
Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys	
145 150 155 160	
 act cag ccc gag ctg cag tgg gcg tgg act aac atg gag gag tat ata	528

Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile	
165 170 175	
agc gcc tgt ttg aac ctg gcc gag cgc aaa cgg ctc gtg gcg cag cac	576
Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His	
180 185 190	
ctg acc cac gtc agc cag acc cag gag cag aac aag gag aat ctg aac	624
Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn	
195 200 205	
ccc aat tct gac gcg cct gtc atc cgg tca aaa acc tcc gcg cgc tac	672
Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr	
210 215 220	
atg gag ctg gtc ggg tgg ctg gtg gac cgg ggc atc acc tcc gag aag	720
Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys	
225 230 235 240	
cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct	768
Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala	
245 250 255	
tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag	816
Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys	
260 265 270	
atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct	864
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala	
275 280 285	
ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg	912
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu	
290 295 300	
aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc	960
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala	
305 310 315 320	
cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccg gcc	1008
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala	
325 330 335	
acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc	1056
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro	
340 345 350	
ttc tac ggc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat	1104

Phe	Tyr	Gly	Cys	Val	Asn	Trp	Thr	Asn	Glu	Asn	Phe	Pro	Phe	Asn	Asp		
		355					360					365					
tgc	gtc	gac	aag	atg	gtg	atc	tgg	tgg	gag	gag	ggc	aag	atg	acg	gcc	1152	
Cys	Val	Asp	Lys	Met	Val	Ile	Trp	Trp	Glu	Glu	Gly	Lys	Met	Thr	Ala		
		370				375					380						
aag	gtc	gtg	gag	tcc	gcc	aag	gcc	att	ctc	ggc	ggc	agc	aag	gtg	cgc	1200	
Lys	Val	Val	Glu	Ser	Ala	Lys	Ala	Ile	Leu	Gly	Gly	Ser	Lys	Val	Arg		
385					390					395					400		
gtg	gac	caa	aag	tgc	aag	tcg	tcc	gcc	cag	atc	gac	ccc	acc	ccc	gtg	1248	
Val	Asp	Gln	Lys	Cys	Lys	Ser	Ser	Ala	Gln	Ile	Asp	Pro	Thr	Pro	Val		
			405						410					415			
atc	gtc	acc	tcc	aac	acc	aac	atg	tgc	gcc	gtg	att	gac	ggg	aac	agc	1296	
Ile	Val	Thr	Ser	Asn	Thr	Asn	Met	Cys	Ala	Val	Ile	Asp	Gly	Asn	Ser		
			420					425					430				
acc	acc	ttc	gag	cac	cag	cag	ccg	ttg	cag	gac	cgg	atg	ttc	aaa	ttt	1344	
Thr	Thr	Phe	Glu	His	Gln	Gln	Pro	Leu	Gln	Asp	Arg	Met	Phe	Lys	Phe		
		435					440					445					
gaa	ctc	acc	cgc	cgt	ctg	gag	cat	gac	ttt	ggc	aag	gtg	aca	aag	cag	1392	
Glu	Leu	Thr	Arg	Arg	Leu	Glu	His	Asp	Phe	Gly	Lys	Val	Thr	Lys	Gln		
	450					455					460						
gaa	gtc	aaa	gag	ttc	ttc	cgc	tgg	gcg	cag	gat	cac	gtg	acc	gag	gtg	1440	
Glu	Val	Lys	Glu	Phe	Phe	Arg	Trp	Ala	Gln	Asp	His	Val	Thr	Glu	Val		
465					470				475					480			
gcg	cat	gag	ttc	tac	gtc	aga	aag	ggt	gga	gcc	aac	aaa	aga	ccc	gcc	1488	
Ala	His	Glu	Phe	Tyr	Val	Arg	Lys	Gly	Gly	Ala	Asn	Lys	Arg	Pro	Ala		
			485					490					495				
ccc	gat	gac	gcg	gat	aaa	agc	gag	ccc	aag	cgg	gcc	tgc	ccc	tca	gtc	1536	
Pro	Asp	Asp	Ala	Asp	Lys	Ser	Glu	Pro	Lys	Arg	Ala	Cys	Pro	Ser	Val		
			500					505					510				
gcg	gat	cca	tcg	acg	tca	gac	gcg	gaa	gga	gct	ccg	gtg	gac	ttt	gcc	1584	
Ala	Asp	Pro	Ser	Thr	Ser	Asp	Ala	Glu	Gly	Ala	Pro	Val	Asp	Phe	Ala		
		515					520					525					
gac	agg	tac	caa	aac	aaa	tgt	tct	cgt	cac	gcg	ggc	atg	ctt	cag	atg	1632	
Asp	Arg	Tyr	Gln	Asn	Lys	Cys	Ser	Arg	His	Ala	Gly	Met	Leu	Gln	Met		
	530					535					540						
ctg	ttt	ccc	tgc	aag	aca	tgc	gag	aga	atg	aat	cag	aat	ttc	aac	att	1680	

Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile
 545 550 555 560

 tgc ttc acg cac ggg acg aga gac tgt tca gag tgc ttc ccc ggc gtg 1728
 Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val
 565 570 575

 tca gaa tct caa ccg gtc gtc aga aag agg acg tat cgg aaa ctc tgt 1776
 Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys
 580 585 590

 gcc att cat cat ctg ctg ggg cgg gct ccc gag att gct tgc tcg gcc 1824
 Ala Ile His His Leu Leu Gly Arg Ala Pro Glu Ile Ala Cys Ser Ala
 595 600 605

 tgc gat ctg gtc aac gtg gac ctg gat gac tgt gtt tct gag caa taa 1872
 Cys Asp Leu Val Asn Val Asp Leu Asp Asp Cys Val Ser Glu Gln
 610 615 620

 <210> 5
 <211> 623
 <212> PRT
 <213> AAV-1

 <400> 5
 Met Pro Gly Phe Tyr Glu Ile Val Ile Lys Val Pro Ser Asp Leu Asp
 1 5 10 15

 Glu His Leu Pro Gly Ile Ser Asp Ser Phe Val Ser Trp Val Ala Glu
 20 25 30

 Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile
 35 40 45

 Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
 50 55 60

 Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
 65 70 75 80

 Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu
 85 90 95

 Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
 100 105 110

 Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu

115	120	125
Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly		
130	135	140
Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys		
145	150	155
Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile		
165	170	175
Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His		
180	185	190
Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn		
195	200	205
Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr		
210	215	220
Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys		
225	230	235
Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala		
245	250	255
Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys		
260	265	270
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala		
275	280	285
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu		
290	295	300
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala		
305	310	315
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala		
325	330	335
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro		
340	345	350
Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp		
355	360	365
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala		

370	375	380
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg		
385	390	395 400
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val		
	405	410 415
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser		
	420	425 430
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe		
	435	440 445
Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln		
	450	455 460
Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val		
	465	470 475 480
Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala		
	485	490 495
Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val		
	500	505 510
Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala		
	515	520 525
Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met		
	530	535 540
Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile		
	545	550 555 560
Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val		
	565	570 575
Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys		
	580	585 590
Ala Ile His His Leu Leu Gly Arg Ala Pro Glu Ile Ala Cys Ser Ala		
	595	600 605
Cys Asp Leu Val Asn Val Asp Leu Asp Asp Cys Val Ser Glu Gln		
	610	615 620

<210> 6

<211> 1641

<212> DNA

<213> AAV-1

<220>

<221> CDS

<222> (1)..(1638)

<400> 6

atg ccg ggc ttc tac gag atc gtg atc aag gtg ccg agc gac ctg gac 48
 Met Pro Gly Phe Tyr Glu Ile Val Ile Lys Val Pro Ser Asp Leu Asp

1 5 10 15

gag cac ctg ccg ggc att tct gac tcg ttt gtg agc tgg gtg gcc gag 96
 Glu His Leu Pro Gly Ile Ser Asp Ser Phe Val Ser Trp Val Ala Glu

20 25 30

aag gaa tgg gag ctg ccc ccg gat tct gac atg gat ctg aat ctg att 144
 Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile

35 40 45

gag cag gca ccc ctg acc gtg gcc gag aag ctg cag cgc gac ttc ctg 192
 Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu

50 55 60

gtc caa tgg cgc cgc gtg agt aag gcc ccg gag gcc ctc ttc ttt gtt 240
 Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val

65 70 75 80

cag ttc gag aag ggc gag tcc tac ttc cac ctc cat att ctg gtg gag 288
 Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu

85 90 95

acc acg ggg gtc aaa tcc atg gtg ctg ggc cgc ttc ctg agt cag att 336
 Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile

100 105 110

agg gac aag ctg gtg cag acc atc tac cgc ggg atc gag ccg acc ctg 384
 Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu

115 120 125

ccc aac tgg ttc gcg gtg acc aag acg cgt aat ggc gcc gga ggg ggg 432
 Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly

130 135 140

aac aag gtg gtg gac gag tgc tac atc ccc aac tac ctc ctg ccc aag 480
 Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys

145	150	155	160	
act cag ccc gag ctg cag tgg gcg tgg act aac atg gag gag tat ata				528
Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile				
	165	170	175	
agc gcc tgt ttg aac ctg gcc gag cgc aaa cgg ctc gtg gcg cag cac				576
Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His				
	180	185	190	
ctg acc cac gtc agc cag acc cag gag cag aac aag gag aat ctg aac				624
Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn				
	195	200	205	
ccc aat tct gac gcg cct gtc atc cgg tca aaa acc tcc gcg cgc tac				672
Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr				
	210	215	220	
atg gag ctg gtc ggg tgg ctg gtg gac cgg ggc atc acc tcc gag aag				720
Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys				
	225	230	235	240
cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct				768
Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala				
	245	250	255	
tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag				816
Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys				
	260	265	270	
atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct				864
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala				
	275	280	285	
ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg				912
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu				
	290	295	300	
aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc				960
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala				
	305	310	315	320
cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccg gcc				1008
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala				
	325	330	335	
acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc				1056
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro				

340	345	350	
ttc tac ggc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat			1104
Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp			
355	360	365	
tgc gtc gac aag atg gtg atc tgg tgg gag gag ggc aag atg acg gcc			1152
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala			
370	375	380	
aag gtc gtg gag tcc gcc aag gcc att ctc ggc ggc agc aag gtg cgc			1200
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg			
385	390	395	400
gtg gac caa aag tgc aag tcg tcc gcc cag atc gac ccc acc ccc gtg			1248
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val			
405	410	415	
atc gtc acc tcc aac acc aac atg tgc gcc gtg att gac ggc aac agc			1296
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser			
420	425	430	
acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt			1344
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe			
435	440	445	
gaa ctc acc cgc cgt ctg gag cat gac ttt ggc aag gtg aca aag cag			1392
Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln			
450	455	460	
gaa gtc aaa gag ttc ttc cgc tgg gcg cag gat cac gtg acc gag gtg			1440
Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val			
465	470	475	480
gcg cat gag ttc tac gtc aga aag ggt gga gcc aac aaa aga ccc gcc			1488
Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala			
485	490	495	
ccc gat gac gcg gat aaa agc gag ccc aag cgg gcc tgc ccc tca gtc			1536
Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val			
500	505	510	
gcg gat cca tcg acg tca gac gcg gaa gga gct ccg gtg gac ttt gcc			1584
Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala			
515	520	525	
gac agg tat ggc tgc cga tgg tta tct tcc aga ttg gct cga gga caa			1632
Asp Arg Tyr Gly Cys Arg Trp Leu Ser Ser Arg Leu Ala Arg Gly Gln			

530

535

540

cct ctc tga

1641

Pro Leu

545

<210> 7

<211> 546

<212> PRT

<213> AAV-1

<400> 7

Met Pro Gly Phe Tyr Glu Ile Val Ile Lys Val Pro Ser Asp Leu Asp

1

5

10

15

Glu His Leu Pro Gly Ile Ser Asp Ser Phe Val Ser Trp Val Ala Glu

20

25

30

Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile

35

40

45

Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu

50

55

60

Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val

65

70

75

80

Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu

85

90

95

Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile

100

105

110

Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu

115

120

125

Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly

130

135

140

Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys

145

150

155

160

Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile

165

170

175

Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His

180

185

190

Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn
 195 200 205
 Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr
 210 215 220
 Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
 225 230 235 240
 Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 245 250 255
 Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
 260 265 270
 Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
 275 280 285
 Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
 290 295 300
 Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
 305 310 315 320
 Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
 325 330 335
 Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
 340 345 350
 Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
 355 360 365
 Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
 370 375 380
 Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
 385 390 395 400
 Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
 405 410 415
 Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
 420 425 430
 Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
 435 440 445

Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
 450 455 460

Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
 465 470 475 480

Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
 485 490 495

Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
 500 505 510

Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
 515 520 525

Asp Arg Tyr Gly Cys Arg Trp Leu Ser Ser Arg Leu Ala Arg Gly Gln
 530 535 540

Pro Leu
 545

<210> 8
 <211> 1200
 <212> DNA
 <213> AAV-1

<220>
 <221> CDS
 <222> (1)..(1197)

<400> 8
 atg gag ctg gtc ggg tgg ctg gtg gac cgg ggc atc acc tcc gag aag 48
 Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
 1 5 10 15

cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct 96
 Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 20 25 30

tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag 144
 Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
 35 40 45

atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct 192
 Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
 50 55 60

ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg 240
 Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
 65 70 75 80

aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc 288
 Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
 85 90 95

cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccg gcc 336
 Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
 100 105 110

acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc 384
 Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
 115 120 125

ttc tac ggc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat 432
 Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
 130 135 140

tgc gtc gac aag atg gtg atc tgg tgg gag gag ggc aag atg acg gcc 480
 Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
 145 150 155 160

aag gtc gtg gag tcc gcc aag gcc att ctc ggc ggc agc aag gtg cgc 528
 Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
 165 170 175

gtg gac caa aag tgc aag tcg tcc gcc cag atc gac ccc acc ccc gtg 576
 Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
 180 185 190

atc gtc acc tcc aac acc aac atg tgc gcc gtg att gac ggg aac agc 624
 Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
 195 200 205

acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt 672
 Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
 210 215 220

gaa ctc acc cgc cgt ctg gag cat gac ttt ggc aag gtg aca aag cag 720
 Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
 225 230 235 240

gaa gtc aaa gag ttc ttc cgc tgg gcg cag gat cac gtg acc gag gtg 768
 Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
 245 250 255

gcg cat gag ttc tac gtc aga aag ggt gga gcc aac aaa aga ccc gcc 816
 Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
 260 265 270

ccc gat gac gcg gat aaa agc gag ccc aag cgg gcc tgc ccc tca gtc 864
 Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
 275 280 285

gcg gat cca tcg acg tca gac gcg gaa gga gct ccg gtg gac ttt gcc 912
 Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
 290 295 300

gac agg tac caa aac aaa tgt tct cgt cac gcg ggc atg ctt cag atg 960
 Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met
 305 310 315 320

ctg ttt ccc tgc aag aca tgc gag aga atg aat cag aat ttc aac att 1008
 Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile
 325 330 335

tgc ttc acg cac ggg acg aga gac tgt tca gag tgc ttc ccc ggc gtg 1056
 Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val
 340 345 350

tca gaa tct caa ccg gtc gtc aga aag agg acg tat cgg aaa ctc tgt 1104
 Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys
 355 360 365

gcc att cat cat ctg ctg ggg cgg gct ccc gag att gct tgc tcg gcc 1152
 Ala Ile His His Leu Leu Gly Arg Ala Pro Glu Ile Ala Cys Ser Ala
 370 375 380

tgc gat ctg gtc aac gtg gac ctg gat gac tgt gtt tct gag caa taa 1200
 Cys Asp Leu Val Asn Val Asp Leu Asp Asp Cys Val Ser Glu Gln
 385 390 395

<210> 9

<211> 399

<212> PRT

<213> AAV-1

<400> 9

Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
 1 5 10 15

Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala

29

275

280

285

Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
 290 295 300

Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met
 305 310 315 320

Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile
 325 330 335

Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val
 340 345 350

Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys
 355 360 365

Ala Ile His His Leu Leu Gly Arg Ala Pro Glu Ile Ala Cys Ser Ala
 370 375 380

Cys Asp Leu Val Asn Val Asp Leu Asp Asp Cys Val Ser Glu Gln
 385 390 395

<210> 10

<211> 969

<212> DNA

<213> AAV-1

<220>

<221> CDS

<222> (1)..(966)

<220>

<221> misc_feature

<222> (943)..(944)

<223> minor splice site

<400> 10

atg gag ctg gtc ggg tgg ctg gtg gac cgg ggc atc acc tcc gag aag 48
 Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
 1 5 10 15

cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct 96
 Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 20 25 30

tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag 144

```

Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
      35              40              45

atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct   192
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
      50              55              60

ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg   240
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
      65              70              75              80

aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc   288
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
      85              90              95

cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccg gcc   336
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
      100             105             110

acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc   384
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
      115             120             125

ttc tac ggc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat   432
Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
      130             135             140

tgc gtc gac aag atg gtg atc tgg tgg gag gag ggc aag atg acg gcc   480
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
      145             150             155             160

aag gtc gtg gag tcc gcc aag gcc att ctc ggc ggc agc aag gtg cgc   528
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
      165             170             175

gtg gac caa aag tgc aag tcg tcc gcc cag atc gac ccc acc ccc gtg   576
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
      180             185             190

atc gtc acc tcc aac acc aac atg tgc gcc gtg att gac ggg aac agc   624
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
      195             200             205

acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt   672
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
      210             215             220

gaa ctc acc cgc cgt ctg gag cat gac ttt ggc aag gtg aca aag cag   720

```


Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
 225 230 235 240

 gaa gtc aaa gag ttc ttc cgc tgg gcg cag gat cac gtg acc gag gtg 768
 Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
 245 250 255

 gcg cat gag ttc tac gtc aga aag ggt gga gcc aac aaa aga ccc gcc 816
 Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
 260 265 270

 ccc gat gac gcg gat aaa agc gag ccc aag cgg gcc tgc ccc tca gtc 864
 Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
 275 280 285

 gcg gat cca tcg acg tca gac gcg gaa gga gct ccg gtg gac ttt gcc 912
 Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
 290 295 300

 gac agg tat ggc tgc cga tgg tta tct tcc aga ttg gct cga gga caa 960
 Asp Arg Tyr Gly Cys Arg Trp Leu Ser Ser Arg Leu Ala Arg Gly Gln
 305 310 315 320

 cct ctc tga 969
 Pro Leu

<210> 11
 <211> 322
 <212> PRT
 <213> AAV-1

<400> 11
 Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
 1 5 10 15

 Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 20 25 30

 Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
 35 40 45

 Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
 50 55 60

 Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
 65 70 75 80

Pro Leu

<210> 12
 <211> 2211
 <212> DNA
 <213> AAV-1

<220>
 <221> CDS
 <222> (1)..(2208)

<400> 12

```

atg gct gcc gat ggt tat ctt cca gat tgg ctc gag gac aac ctc tct   48
Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
   1             5             10             15

gag ggc att cgc gag tgg tgg gac ttg aaa cct gga gcc ccg aag ccc   96
Glu Gly Ile Arg Glu Trp Trp Asp Leu Lys Pro Gly Ala Pro Lys Pro
           20           25           30

aaa gcc aac cag caa aag cag gac gac ggc cgg ggt ctg gtg ctt cct   144
Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro
           35           40           45

ggc tac aag tac ctc gga ccc ttc aac gga ctc gac aag ggg gag ccc   192
Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
           50           55           60

gtc aac gcg gcg gac gca gcg gcc ctc gag cac gac aag gcc tac gac   240
Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
           65           70           75           80

cag cag ctc aaa gcg ggt gac aat ccg tac ctg cgg tat aac cac gcc   288
Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
           85           90           95

gac gcc gag ttt cag gag cgt ctg caa gaa gat acg tct ttt ggg ggc   336
Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
           100          105          110

aac ctc ggg cga gca gtc ttc cag gcc aag aag cgg gtt ctc gaa cct   384
Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
           115          120          125

ctc ggt ctg gtt gag gaa ggc gct aag acg gct cct gga aag aaa cgt   432
Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
           130          135          140

ccg gta gag cag tcg cca caa gag cca gac tcc tcc tcg ggc atc ggc   480

```

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly
 145 150 155 160

 aag aca ggc cag cag ccc gct aaa aag aga ctc aat ttt ggt cag act 528
 Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
 165 170 175

 ggc gac tca gag tca gtc ccc gat cca caa cct ctc gga gaa cct cca 576
 Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro
 180 185 190

 gca acc ccc gct gct gtg gga cct act aca atg gct tca ggc ggt ggc 624
 Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
 195 200 205

 gca cca atg gca gac aat aac gaa ggc gcc gac gga gtg ggt aat gcc 672
 Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala
 210 215 220

 tca gga aat tgg cat tgc gat tcc aca tgg ctg ggc gac aga gtc atc 720
 Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile
 225 230 235 240

 acc acc agc acc cgc acc tgg gcc ttg ccc acc tac aat aac cac ctc 768
 Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
 245 250 255

 tac aag caa atc tcc agt gct tca acg ggg gcc agc aac gac aac cac 816
 Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His
 260 265 270

 tac ttc ggc tac agc acc ccc tgg ggg tat ttt gat ttc aac aga ttc 864
 Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe
 275 280 285

 cac tgc cac ttt tca cca cgt gac tgg cag cga ctc atc aac aac aat 912
 His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn
 290 295 300

 tgg gga ttc cgg ccc aag aga ctc aac ttc aaa ctc ttc aac atc caa 960
 Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln
 305 310 315 320

 gtc aag gag gtc acg acg aat gat ggc gtc aca acc atc gct aat aac 1008
 Val Lys Glu Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn
 325 330 335

 ctt acc agc acg gtt caa gtc ttc tcg gac tcg gag tac cag ctt ccg 1056

Leu Thr Ser Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro
 340 345 350

tac gtc ctc ggc tct gcg cac cag ggc tgc ctc cct ccg ttc ccg gcg 1104
 Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala
 355 360 365

gac gtg ttc atg att ccg caa tac ggc tac ctg acg ctc aac aat ggc 1152
 Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly
 370 375 380

agc caa gcc gtg gga cgt tca tcc ttt tac tgc ctg gaa tat ttc cct 1200
 Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro
 385 390 395 400

tct cag atg ctg aga acg ggc aac aac ttt acc ttc agc tac acc ttt 1248
 Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe
 405 410 415

gag gaa gtg cct ttc cac agc agc tac gcg cac agc cag agc ctg gac 1296
 Glu Glu Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp
 420 425 430

cgg ctg atg aat cct ctc atc gac caa tac ctg tat tac ctg aac aga 1344
 Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Asn Arg
 435 440 445

act caa aat cag tcc gga agt gcc caa aac aag gac ttg ctg ttt agc 1392
 Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser
 450 455 460

cgt ggg tct cca gct ggc atg tct gtt cag ccc aaa aac tgg cta cct 1440
 Arg Gly Ser Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro
 465 470 475 480

gga ccc tgt tat cgg cag cag cgc gtt tct aaa aca aaa aca gac aac 1488
 Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn
 485 490 495

aac aac agc aat ttt acc tgg act ggt gct tca aaa tat aac ctc aat 1536
 Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn
 500 505 510

ggg cgt gaa tcc atc atc aac cct ggc act gct atg gcc tca cac aaa 1584
 Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys
 515 520 525

gac gac gaa gac aag ttc ttt ccc atg agc ggt gtc atg att ttt gga 1632

Asp Asp Glu Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe Gly	
530 535 540	
aaa gag agc gcc gga gct tca aac act gca ttg gac aat gtc atg att	1680
Lys Glu Ser Ala Gly Ala Ser Asn Thr Ala Leu Asp Asn Val Met Ile	
545 550 555 560	
aca gac gaa gag gaa att aaa gcc act aac cct gtg gcc acc gaa aga	1728
Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg	
565 570 575	
ttt ggg acc gtg gca gtc aat ttc cag agc agc agc aca gac cct gcg	1776
Phe Gly Thr Val Ala Val Asn Phe Gln Ser Ser Ser Thr Asp Pro Ala	
580 585 590	
acc gga gat gtg cat gct atg gga gca tta cct ggc atg gtg tgg caa	1824
Thr Gly Asp Val His Ala Met Gly Ala Leu Pro Gly Met Val Trp Gln	
595 600 605	
gat aga gac gtg tac ctg cag ggt ccc att tgg gcc aaa att cct cac	1872
Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His	
610 615 620	
aca gat gga cac ttt cac ccg tct cct ctt atg ggc ggc ttt gga ctc	1920
Thr Asp Gly His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu	
625 630 635 640	
aag aac ccg cct cct cag atc ctc atc aaa aac acg cct gtt cct gcg	1968
Lys Asn Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala	
645 650 655	
aat cct ccg gcg gag ttt tca gct aca aag ttt gct tca ttc atc acc	2016
Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr	
660 665 670	
caa tac tcc aca gga caa gtg agt gtg gaa att gaa tgg gag ctg cag	2064
Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln	
675 680 685	
aaa gaa aac agc aag cgc tgg aat ccc gaa gtg cag tac aca tcc aat	2112
Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Val Gln Tyr Thr Ser Asn	
690 695 700	
tat gca aaa tct gcc aac gtt gat ttt act gtg gac aac aat gga ctt	2160
Tyr Ala Lys Ser Ala Asn Val Asp Phe Thr Val Asp Asn Asn Gly Leu	
705 710 715 720	
tat act gag cct cgc ccc att ggc acc cgt tac ctt acc cgt ccc ctg	2208

taa

2211

<210> 13
<211> 736
<212> PRT
<213> AAV-1

```
<400> 13
Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
  1             5             10             15
```

Glu Gly Ile Arg Glu Trp Trp Asp Leu Lys Pro Gly Ala Pro Lys Pro
20 25 30

Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro
35 40 45

Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
50 55 60

Val	Asn	Ala	Ala	Asp	Ala	Ala	Ala	Leu	Glu	His	Asp	Lys	Ala	Tyr	Asp
65					70					75					80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
85 90 95

Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
100 105 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
115 120 125

Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
130 135 140

Pro	Val	Glu	Gln	Ser	Pro	Gln	Glu	Pro	Asp	Ser	Ser	Ser	Gly	Ile	Gly
145					150					155					160

Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
165 170 175

Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro
180 185 190

Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
 195 200 205

Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala
 210 215 220

Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile
 225 230 235 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
 245 250 255

Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His
 260 265 270

Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe
 275 280 285

His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn
 290 295 300

Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln
 305 310 315 320

Val Lys Glu Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn
 325 330 335

Leu Thr Ser Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro
 340 345 350

Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala
 355 360 365

Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly
 370 375 380

Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro
 385 390 395 400

Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe
 405 410 415

Glu Glu Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp
 420 425 430

Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Asn Arg
 435 440 445

Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser
 450 455 460

Arg Gly Ser Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro
 465 470 475 480

Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn
 485 490 495

Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn
 500 505 510

Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys
 515 520 525

Asp Asp Glu Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe Gly
 530 535 540

Lys Glu Ser Ala Gly Ala Ser Asn Thr Ala Leu Asp Asn Val Met Ile
 545 550 555 560

Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg
 565 570 575

Phe Gly Thr Val Ala Val Asn Phe Gln Ser Ser Ser Thr Asp Pro Ala
 580 585 590

Thr Gly Asp Val His Ala Met Gly Ala Leu Pro Gly Met Val Trp Gln
 595 600 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
 610 615 620

Thr Asp Gly His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu
 625 630 635 640

Lys Asn Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
 645 650 655

Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr
 660 665 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
 675 680 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Val Gln Tyr Thr Ser Asn
 690 695 700

Tyr Ala Lys Ser Ala Asn Val Asp Phe Thr Val Asp Asn Asn Gly Leu
705 710 715 720

Tyr Thr Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Pro Leu
725 730 735

<210> 14

<211> 1800

<212> DNA

<213> AAV-1

<220>

<221> CDS

<222> (1)..(1797)

<400> 14

acg gct cct gga aag aaa cgt ccg gta gag cag tcg cca caa gag cca 48
Thr Ala Pro Gly Lys Lys Arg Pro Val Glu Gln Ser Pro Gln Glu Pro
1 5 10 15

gac tcc tcc tcg ggc atc ggc aag aca ggc cag cag ccc gct aaa aag 96
Asp Ser Ser Ser Gly Ile Gly Lys Thr Gly Gln Gln Pro Ala Lys Lys
20 25 30

aga ctc aat ttt ggt cag act ggc gac tca gag tca gtc ccc gat cca 144
Arg Leu Asn Phe Gly Gln Thr Gly Asp Ser Glu Ser Val Pro Asp Pro
35 40 45

caa cct ctc gga gaa cct cca gca acc ccc gct gct gtg gga cct act 192
Gln Pro Leu Gly Glu Pro Pro Ala Thr Pro Ala Ala Val Gly Pro Thr
50 55 60

aca atg gct tca ggc ggt ggc gca cca atg gca gac aat aac gaa ggc 240
Thr Met Ala Ser Gly Gly Gly Ala Pro Met Ala Asp Asn Asn Glu Gly
65 70 75 80

gcc gac gga gtg ggt aat gcc tca gga aat tgg cat tgc gat tcc aca 288
Ala Asp Gly Val Gly Asn Ala Ser Gly Asn Trp His Cys Asp Ser Thr
85 90 95

tgg ctg ggc gac aga gtc atc acc acc agc acc cgc acc tgg gcc ttg 336
Trp Leu Gly Asp Arg Val Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu
100 105 110

ccc acc tac aat aac cac ctc tac aag caa atc tcc agt gct tca acg 384
Pro Thr Tyr Asn Asn His Leu Tyr Lys Gln Ile Ser Ser Ala Ser Thr
115 120 125

ggg gcc agc aac gac aac cac tac ttc ggc tac agc acc ccc tgg ggg 432
 Gly Ala Ser Asn Asp Asn His Tyr Phe Gly Tyr Ser Thr Pro Trp Gly
 130 135 140

tat ttt gat ttc aac aga ttc cac tgc cac ttt tca cca cgt gac tgg 480
 Tyr Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp
 145 150 155 160

cag cga ctc atc aac aac aat tgg gga ttc cgg ccc aag aga ctc aac 528
 Gln Arg Leu Ile Asn Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn
 165 170 175

ttc aaa ctc ttc aac atc caa gtc aag gag gtc acg acg aat gat ggc 576
 Phe Lys Leu Phe Asn Ile Gln Val Lys Glu Val Thr Thr Asn Asp Gly
 180 185 190

gtc aca acc atc gct aat aac ctt acc agc acg gtt caa gtc ttc tcg 624
 Val Thr Thr Ile Ala Asn Asn Leu Thr Ser Thr Val Gln Val Phe Ser
 195 200 205

gac tcg gag tac cag ctt ccg tac gtc ctc ggc tct gcg cac cag ggc 672
 Asp Ser Glu Tyr Gln Leu Pro Tyr Val Leu Gly Ser Ala His Gln Gly
 210 215 220

tgc ctc cct ccg ttc ccg gcg gac gtg ttc atg att ccg caa tac ggc 720
 Cys Leu Pro Pro Phe Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly
 225 230 235 240

tac ctg acg ctc aac aat ggc agc caa gcc gtg gga cgt tca tcc ttt 768
 Tyr Leu Thr Leu Asn Asn Gly Ser Gln Ala Val Gly Arg Ser Ser Phe
 245 250 255

tac tgc ctg gaa tat ttc cct tct cag atg ctg aga acg ggc aac aac 816
 Tyr Cys Leu Glu Tyr Phe Pro Ser Gln Met Leu Arg Thr Gly Asn Asn
 260 265 270

ttt acc ttc agc tac acc ttt gag gaa gtg cct ttc cac agc agc tac 864
 Phe Thr Phe Ser Tyr Thr Phe Glu Glu Val Pro Phe His Ser Ser Tyr
 275 280 285

gcg cac agc cag agc ctg gac cgg ctg atg aat cct ctc atc gac caa 912
 Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln
 290 295 300

tac ctg tat tac ctg aac aga act caa aat cag tcc gga agt gcc caa 960
 Tyr Leu Tyr Tyr Leu Asn Arg Thr Gln Asn Gln Ser Gly Ser Ala Gln
 305 310 315 320

aac aag gac ttg ctg ttt agc cgt ggg tct cca gct ggc atg tct gtt	1008
Asn Lys Asp Leu Leu Phe Ser Arg Gly Ser Pro Ala Gly Met Ser Val	
325 330 335	
cag ccc aaa aac tgg cta cct gga ccc tgt tat cgg cag cag cgc gtt	1056
Gln Pro Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val	
340 345 350	
tct aaa aca aaa aca gac aac aac aac agc aat ttt acc tgg act ggt	1104
Ser Lys Thr Lys Thr Asp Asn Asn Asn Ser Asn Phe Thr Trp Thr Gly	
355 360 365	
gct tca aaa tat aac ctc aat ggg cgt gaa tcc atc atc aac cct ggc	1152
Ala Ser Lys Tyr Asn Leu Asn Gly Arg Glu Ser Ile Ile Asn Pro Gly	
370 375 380	
act gct atg gcc tca cac aaa gac gac gaa gac aag ttc ttt ccc atg	1200
Thr Ala Met Ala Ser His Lys Asp Asp Glu Asp Lys Phe Phe Pro Met	
385 390 395 400	
agc ggt gtc atg att ttt gga aaa gag agc gcc gga gct tca aac act	1248
Ser Gly Val Met Ile Phe Gly Lys Glu Ser Ala Gly Ala Ser Asn Thr	
405 410 415	
gca ttg gac aat gtc atg att aca gac gaa gag gaa att aaa gcc act	1296
Ala Leu Asp Asn Val Met Ile Thr Asp Glu Glu Glu Ile Lys Ala Thr	
420 425 430	
aac cct gtg gcc acc gaa aga ttt ggg acc gtg gca gtc aat ttc cag	1344
Asn Pro Val Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Phe Gln	
435 440 445	
agc agc agc aca gac cct gcg acc gga gat gtg cat gct atg gga gca	1392
Ser Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Ala Met Gly Ala	
450 455 460	
tta cct ggc atg gtg tgg caa gat aga gac gtg tac ctg cag ggt ccc	1440
Leu Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro	
465 470 475 480	
att tgg gcc aaa att cct cac aca gat gga cac ttt cac ccg tct cct	1488
Ile Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro	
485 490 495	
ctt atg ggc ggc ttt gga ctc aag aac ccg cct cct cag atc ctc atc	1536
Leu Met Gly Gly Phe Gly Leu Lys Asn Pro Pro Pro Gln Ile Leu Ile	
500 505 510	

aaa aac acg cct gtt cct gcg aat cct ccg gcg gag ttt tca gct aca 1584
 Lys Asn Thr Pro Val Pro Ala Asn Pro Pro Ala Glu Phe Ser Ala Thr
 515 520 525

aag ttt gct tca ttc atc acc caa tac tcc aca gga caa gtg agt gtg 1632
 Lys Phe Ala Ser Phe Ile Thr Gln Tyr Ser Thr Gly Gln Val Ser Val
 530 535 540

gaa att gaa tgg gag ctg cag aaa gaa aac agc aag cgc tgg aat ccc 1680
 Glu Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro
 545 550 555 560

gaa gtg cag tac aca tcc aat tat gca aaa tct gcc aac gtt gat ttt 1728
 Glu Val Gln Tyr Thr Ser Asn Tyr Ala Lys Ser Ala Asn Val Asp Phe
 565 570 575

act gtg gac aac aat gga ctt tat act gag cct cgc ccc att ggc acc 1776
 Thr Val Asp Asn Asn Gly Leu Tyr Thr Glu Pro Arg Pro Ile Gly Thr
 580 585 590

cgt tac ctt acc cgt ccc ctg taa 1800
 Arg Tyr Leu Thr Arg Pro Leu
 595

<210> 15
 <211> 599
 <212> PRT
 <213> AAV-1

<400> 15
 Thr Ala Pro Gly Lys Lys Arg Pro Val Glu Gln Ser Pro Gln Glu Pro
 1 5 10 15

Asp Ser Ser Ser Gly Ile Gly Lys Thr Gly Gln Gln Pro Ala Lys Lys
 20 25 30

Arg Leu Asn Phe Gly Gln Thr Gly Asp Ser Glu Ser Val Pro Asp Pro
 35 40 45

Gln Pro Leu Gly Glu Pro Pro Ala Thr Pro Ala Ala Val Gly Pro Thr
 50 55 60

Thr Met Ala Ser Gly Gly Gly Ala Pro Met Ala Asp Asn Asn Glu Gly
 65 70 75 80

Ala Asp Gly Val Gly Asn Ala Ser Gly Asn Trp His Cys Asp Ser Thr

85

90

95

Trp Leu Gly Asp Arg Val Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu
 100 105 110

Pro Thr Tyr Asn Asn His Leu Tyr Lys Gln Ile Ser Ser Ala Ser Thr
 115 120 125

Gly Ala Ser Asn Asp Asn His Tyr Phe Gly Tyr Ser Thr Pro Trp Gly
 130 135 140

Tyr Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp
 145 150 155 160

Gln Arg Leu Ile Asn Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn
 165 170 175

Phe Lys Leu Phe Asn Ile Gln Val Lys Glu Val Thr Thr Asn Asp Gly
 180 185 190

Val Thr Thr Ile Ala Asn Asn Leu Thr Ser Thr Val Gln Val Phe Ser
 195 200 205

Asp Ser Glu Tyr Gln Leu Pro Tyr Val Leu Gly Ser Ala His Gln Gly
 210 215 220

Cys Leu Pro Pro Phe Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly
 225 230 235 240

Tyr Leu Thr Leu Asn Asn Gly Ser Gln Ala Val Gly Arg Ser Ser Phe
 245 250 255

Tyr Cys Leu Glu Tyr Phe Pro Ser Gln Met Leu Arg Thr Gly Asn Asn
 260 265 270

Phe Thr Phe Ser Tyr Thr Phe Glu Glu Val Pro Phe His Ser Ser Tyr
 275 280 285

Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln
 290 295 300

Tyr Leu Tyr Tyr Leu Asn Arg Thr Gln Asn Gln Ser Gly Ser Ala Gln
 305 310 315 320

Asn Lys Asp Leu Leu Phe Ser Arg Gly Ser Pro Ala Gly Met Ser Val
 325 330 335

Gln Pro Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val

340	345	350
Ser Lys Thr Lys Thr Asp Asn Asn Asn Ser Asn Phe Thr Trp Thr Gly		
355	360	365
Ala Ser Lys Tyr Asn Leu Asn Gly Arg Glu Ser Ile Ile Asn Pro Gly		
370	375	380
Thr Ala Met Ala Ser His Lys Asp Asp Glu Asp Lys Phe Phe Pro Met		
385	390	395 400
Ser Gly Val Met Ile Phe Gly Lys Glu Ser Ala Gly Ala Ser Asn Thr		
	405	410 415
Ala Leu Asp Asn Val Met Ile Thr Asp Glu Glu Glu Ile Lys Ala Thr		
	420	425 430
Asn Pro Val Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Phe Gln		
	435	440 445
Ser Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Ala Met Gly Ala		
	450	455 460
Leu Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro		
465	470	475 480
Ile Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro		
	485	490 495
Leu Met Gly Gly Phe Gly Leu Lys Asn Pro Pro Pro Gln Ile Leu Ile		
	500	505 510
Lys Asn Thr Pro Val Pro Ala Asn Pro Pro Ala Glu Phe Ser Ala Thr		
	515	520 525
Lys Phe Ala Ser Phe Ile Thr Gln Tyr Ser Thr Gly Gln Val Ser Val		
	530	535 540
Glu Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro		
545	550	555 560
Glu Val Gln Tyr Thr Ser Asn Tyr Ala Lys Ser Ala Asn Val Asp Phe		
	565	570 575
Thr Val Asp Asn Asn Gly Leu Tyr Thr Glu Pro Arg Pro Ile Gly Thr		
	580	585 590
Arg Tyr Leu Thr Arg Pro Leu		

595

<210> 16

<211> 1605

<212> DNA

<213> AAV-1

<220>

<221> CDS

<222> (1)..(1602)

<400> 16

atg gct tca ggc ggt ggc gca cca atg gca gac aat aac gaa ggc gcc 48
 Met Ala Ser Gly Gly Gly Ala Pro Met Ala Asp Asn Asn Glu Gly Ala
 1 5 10 15

gac gga gtg ggt aat gcc tca gga aat tgg cat tgc gat tcc aca tgg 96
 Asp Gly Val Gly Asn Ala Ser Gly Asn Trp His Cys Asp Ser Thr Trp
 20 25 30

ctg ggc gac aga gtc atc acc acc agc acc cgc acc tgg gcc ttg ccc 144
 Leu Gly Asp Arg Val Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro
 35 40 45

acc tac aat aac cac ctc tac aag caa atc tcc agt gct tca acg ggg 192
 Thr Tyr Asn Asn His Leu Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly
 50 55 60

gcc agc aac gac aac cac tac ttc ggc tac agc acc ccc tgg ggg tat 240
 Ala Ser Asn Asp Asn His Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr
 65 70 75 80

ttt gat ttc aac aga ttc cac tgc cac ttt tca cca cgt gac tgg cag 288
 Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp Gln
 85 90 95

cga ctc atc aac aac aat tgg gga ttc cgg ccc aag aga ctc aac ttc 336
 Arg Leu Ile Asn Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe
 100 105 110

aaa ctc ttc aac atc caa gtc aag gag gtc acg acg aat gat ggc gtc 384
 Lys Leu Phe Asn Ile Gln Val Lys Glu Val Thr Thr Asn Asp Gly Val
 115 120 125

aca acc atc gct aat aac ctt acc agc acg gtt caa gtc ttc tcg gac 432
 Thr Thr Ile Ala Asn Asn Leu Thr Ser Thr Val Gln Val Phe Ser Asp
 130 135 140

tcg gag tac cag ctt ccg tac gtc ctc ggc tct gcg cac cag ggc tgc	480
Ser Glu Tyr Gln Leu Pro Tyr Val Leu Gly Ser Ala His Gln Gly Cys	
145 150 155 160	
ctc cct ccg ttc ccg gcg gac gtg ttc atg att ccg caa tac ggc tac	528
Leu Pro Pro Phe Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr	
165 170 175	
ctg acg ctc aac aat ggc agc caa gcc gtg gga cgt tca tcc ttt tac	576
Leu Thr Leu Asn Asn Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr	
180 185 190	
tgc ctg gaa tat ttc cct tct cag atg ctg aga acg ggc aac aac ttt	624
Cys Leu Glu Tyr Phe Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe	
195 200 205	
acc ttc agc tac acc ttt gag gaa gtg cct ttc cac agc agc tac gcg	672
Thr Phe Ser Tyr Thr Phe Glu Glu Val Pro Phe His Ser Ser Tyr Ala	
210 215 220	
cac agc cag agc ctg gac cgg ctg atg aat cct ctc atc gac caa tac	720
His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr	
225 230 235 240	
ctg tat tac ctg aac aga act caa aat cag tcc gga agt gcc caa aac	768
Leu Tyr Tyr Leu Asn Arg Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn	
245 250 255	
aag gac ttg ctg ttt agc cgt ggg tct cca gct ggc atg tct gtt cag	816
Lys Asp Leu Leu Phe Ser Arg Gly Ser Pro Ala Gly Met Ser Val Gln	
260 265 270	
ccc aaa aac tgg cta cct gga ccc tgt tat cgg cag cag cgc gtt tct	864
Pro Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser	
275 280 285	
aaa aca aaa aca gac aac aac aac agc aat ttt acc tgg act ggt gct	912
Lys Thr Lys Thr Asp Asn Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala	
290 295 300	
tca aaa tat aac ctc aat ggg cgt gaa tcc atc atc aac cct ggc act	960
Ser Lys Tyr Asn Leu Asn Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr	
305 310 315 320	
gct atg gcc tca cac aaa gac gac gaa gac aag ttc ttt ccc atg agc	1008
Ala Met Ala Ser His Lys Asp Asp Glu Asp Lys Phe Phe Pro Met Ser	
325 330 335	

ggt gtc atg att ttt gga aaa gag agc gcc gga gct tca aac act gca 1056
 Gly Val Met Ile Phe Gly Lys Glu Ser Ala Gly Ala Ser Asn Thr Ala
 340 345 350

ttg gac aat gtc atg att aca gac gaa gag gaa att aaa gcc act aac 1104
 Leu Asp Asn Val Met Ile Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn
 355 360 365

cct gtg gcc acc gaa aga ttt ggg acc gtg gca gtc aat ttc cag agc 1152
 Pro Val Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Phe Gln Ser
 370 375 380

agc agc aca gac cct gcg acc gga gat gtg cat gct atg gga gca tta 1200
 Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Ala Met Gly Ala Leu
 385 390 395 400

cct ggc atg gtg tgg caa gat aga gac gtg tac ctg cag ggt ccc att 1248
 Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile
 405 410 415

tgg gcc aaa att cct cac aca gat gga cac ttt cac ccg tct cct ctt 1296
 Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro Leu
 420 425 430

atg ggc ggc ttt gga ctc aag aac ccg cct cct cag atc ctc atc aaa 1344
 Met Gly Gly Phe Gly Leu Lys Asn Pro Pro Pro Gln Ile Leu Ile Lys
 435 440 445

aac acg cct gtt cct gcg aat cct ccg gcg gag ttt tca gct aca aag 1392
 Asn Thr Pro Val Pro Ala Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys
 450 455 460

ttt gct tca ttc atc acc caa tac tcc aca gga caa gtg agt gtg gaa 1440
 Phe Ala Ser Phe Ile Thr Gln Tyr Ser Thr Gly Gln Val Ser Val Glu
 465 470 475 480

att gaa tgg gag ctg cag aaa gaa aac agc aag cgc tgg aat ccc gaa 1488
 Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu
 485 490 495

gtg cag tac aca tcc aat tat gca aaa tct gcc aac gtt gat ttt act 1536
 Val Gln Tyr Thr Ser Asn Tyr Ala Lys Ser Ala Asn Val Asp Phe Thr
 500 505 510

gtg gac aac aat gga ctt tat act gag cct cgc ccc att ggc acc cgt 1584
 Val Asp Asn Asn Gly Leu Tyr Thr Glu Pro Arg Pro Ile Gly Thr Arg
 515 520 525

tac ctt acc cgt ccc ctg taa
 Tyr Leu Thr Arg Pro Leu
 530

1605

<210> 17
 <211> 534
 <212> PRT
 <213> AAV-1

<400> 17

Met Ala Ser Gly Gly Gly Ala Pro Met Ala Asp Asn Asn Glu Gly Ala
 1 5 10 15

Asp Gly Val Gly Asn Ala Ser Gly Asn Trp His Cys Asp Ser Thr Trp
 20 25 30

Leu Gly Asp Arg Val Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro
 35 40 45

Thr Tyr Asn Asn His Leu Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly
 50 55 60

Ala Ser Asn Asp Asn His Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr
 65 70 75 80

Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp Gln
 85 90 95

Arg Leu Ile Asn Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe
 100 105 110

Lys Leu Phe Asn Ile Gln Val Lys Glu Val Thr Thr Asn Asp Gly Val
 115 120 125

Thr Thr Ile Ala Asn Asn Leu Thr Ser Thr Val Gln Val Phe Ser Asp
 130 135 140

Ser Glu Tyr Gln Leu Pro Tyr Val Leu Gly Ser Ala His Gln Gly Cys
 145 150 155 160

Leu Pro Pro Phe Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr
 165 170 175

Leu Thr Leu Asn Asn Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr
 180 185 190

Cys Leu Glu Tyr Phe Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe
 195 200 205
 Thr Phe Ser Tyr Thr Phe Glu Glu Val Pro Phe His Ser Ser Tyr Ala
 210 215 220
 His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr
 225 230 235 240
 Leu Tyr Tyr Leu Asn Arg Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn
 245 250 255
 Lys Asp Leu Leu Phe Ser Arg Gly Ser Pro Ala Gly Met Ser Val Gln
 260 265 270
 Pro Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser
 275 280 285
 Lys Thr Lys Thr Asp Asn Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala
 290 295 300
 Ser Lys Tyr Asn Leu Asn Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr
 305 310 315 320
 Ala Met Ala Ser His Lys Asp Asp Glu Asp Lys Phe Phe Pro Met Ser
 325 330 335
 Gly Val Met Ile Phe Gly Lys Glu Ser Ala Gly Ala Ser Asn Thr Ala
 340 345 350
 Leu Asp Asn Val Met Ile Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn
 355 360 365
 Pro Val Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Phe Gln Ser
 370 375 380
 Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Ala Met Gly Ala Leu
 385 390 395 400
 Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile
 405 410 415
 Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro Leu
 420 425 430
 Met Gly Gly Phe Gly Leu Lys Asn Pro Pro Pro Gln Ile Leu Ile Lys
 435 440 445

Asn Thr Pro Val Pro Ala Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys
 450 455 460

Phe Ala Ser Phe Ile Thr Gln Tyr Ser Thr Gly Gln Val Ser Val Glu
 465 470 475 480

Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu
 485 490 495

Val Gln Tyr Thr Ser Asn Tyr Ala Lys Ser Ala Asn Val Asp Phe Thr
 500 505 510

Val Asp Asn Asn Gly Leu Tyr Thr Glu Pro Arg Pro Ile Gly Thr Arg
 515 520 525

Tyr Leu Thr Arg Pro Leu
 530

<210> 18
 <211> 4681
 <212> DNA
 <213> aav-2

<400> 18
 ttggccactc cctctctgcg cgcctcgcgc ctcactgagg ccgggcgacc aaaggtcgcc 60
 cgacgcccgg gctttgcccg ggccggcctca gtgagcgagc gagcgcgag agaggggagt 120
 gccaaactcca tcactagggg ttcctggagg ggtggagtcg tgacgtgaat tacgtcatag 180
 ggtagggag gtctgtatt agaggtcacg tgagtgtttt gcgacatttt gcgacaccat 240
 gtggtcacgc tgggtattta agcccagtg agcacgcagg gtctccattt tgaagcggga 300
 ggtttgaacg cgcagccgcc atgccgggt tttacgagat tgtgattaag gtccccagcg 360
 accttgacgg gcactcgcgc ggcatttctg acagctttgt gaactgggtg gccgagaagg 420
 aatgggagtt gccgccagat tctgacatgg atctgaatct gattgagcag gcacccctga 480
 ccgtggccga gaagctgcag cgcgactttc tgacggaatg gcgccgtgtg agtaaggccc 540
 cggaggccct tttctttgtg caatttgaga agggagagag ctacttccac atgcacgtgc 600
 tcgtggaac caccggggtg aaatccatgg tttgggacg tttcctgagt cagattcgcg 660
 aaaaactgat tcagagaatt taccgcggga tcgagccgac tttgcaaac tggttcgcgg 720

tcacaaagac cagaaatggc gccggaggcg ggaacaaggt ggtggatgag tgctacatcc 780
ccaattactt gtcceccaaa acccagcctg agctccagt ggcgtggact aatatggaac 840
agtatttaag cgctgtttg aatctcacgg agcgtaaacg gttggtggcg cagcatctga 900
cgcacgtgtc gcagacgcag gagcagaaca aagagaatca gaatcccaat tctgatgcgc 960
cggtgatcag atcaaaaact tcagccaggt acatggagct ggtcgggtgg ctctgggaca 1020
aggggattac ctcggaagaag cagtggatcc aggaggacca ggctcatatc atctccttca 1080
atgcggcctc caactcgcg tcccaaatca aggtgcctt ggacaatgcg ggaaagatta 1140
tgagcctgac taaaaccgcc ccgactacc tgggtggcca gcagcccgtg gaggacattt 1200
ccagcaatcg gatattataa attttgaac taaacgggta cgatcccaa tatgcggctt 1260
ccgtctttct gggatgggcc acgaaaaagt tcggcaagag gaacaccatc tggctgtttg 1320
ggcctgcaac taccgggaag accaaccatc cgaggccat agcccacact gtgcccttct 1380
acgggtgcgt aaactggacc aatgagaact ttcccttcaa cgactgtgtc gacaagatgg 1440
tgatctggtg ggaggagggg aagatgaccg ccaaggtcgt ggagtcggcc aaagccattc 1500
tcggaggaag caaggtgcgc gtggaccaga aatgcaagtc ctcggccag atagaccga 1560
ctcccgtgat cgtcacctcc aacaccaaca tgtgcgccgt gattgacggg aactcaacga 1620
ccttcgaaca ccagcagccg ttgcaagacc ggatgttcaa atttgaactc acccgccgtc 1680
tggatcatga ctttggaag gtcaccaagc aggaagtcaa agacttttc cggtgggcaa 1740
aggatcacgt ggttgaggtg gagcatgaat tctacgtcaa aaagggtgga gccaaagaaa 1800
gacccgcccc cagtgcgca gatataagt agccaaaacg ggtgcgcgag tcagttgcgc 1860
agccatcgac gtcagacgcg gaagcttcga tcaactacgc agacaggtac caaaacaaat 1920
gttctcgtca cgtgggcatg aatctgatgc tgtttcctg cagacaatgc gagagaatga 1980
atcagaattc aaatatctgc ttcactcacg gacagaaaga ctgttttagag tgctttcccg 2040
tgtcagaatc tcaaccggtt tctgtcgtca aaaaggcgta tcagaaactg tgctacattc 2100
atcatatcat gggaaagggt ccagacgctt gcaactgcctg cgatctggtc aatgtggatt 2160

tggatgactg catctttgaa caataaatga tttaaatacag gtatggctgc cgatgggttat 2220
cttccagatt ggctcgagga cactctctct gaaggaataa gacagtgggtg gaagctcaaa 2280
cctggcccac caccacaaa gccgcagag cggcataagg acgacagcag gggctcttggtg 2340
cttcctgggt acaagtacct cggacccttc aacggactcg acaagggaga gccgggtcaac 2400
gaggcagacg ccgcggccct cgagcacgac aaagcctacg accggcagct cgacagcggg 2460
gacaaccctg acctcaagta caaccacgcc gacgcggagt ttcaggagcg ccttaaagaa 2520
gatacgtctt ttgggggcaa cctcggacga gcagtcttcc aggcgaaaaa gaggggttctt 2580
gaacctctcg gcctggttga ggaacctgtt aagacggctc cgggaaaaaa gaggccggta 2640
gagcactctc ctgtggagcc agactcctcc tcgggaaccg gaaagccggg ccagcagcct 2700
gcaagaaaaa gattgaattt tggtcagact ggagacgcag actcagtacc tgacccccag 2760
cctctcggac agccaccagc agccccctct ggtctgggaa ctaatacgat ggctacaggc 2820
agtggcgcac caatggcaga caataacgag ggcgccgacg gagtgggtaa ttcctccgga 2880
aattggcatt gcgattccac atggatgggc gacagagtca tcaccaccag caccgaacc 2940
tgggccctgc ccacctacaa caaccacctc tacaacaaa tttccagcca atcaggagcc 3000
tcgaacgaca atcactactt tggctacagc accccttggg ggtattttga cttcaacaga 3060
ttccactgcc acttttcacc acgtgactgg caaagactca tcaacaacaa ctggggattc 3120
cgaccaaga gactcaactt caacctcttt aacattcaag tcaaagaggt cacgcagaat 3180
gacggtacga cgacgattgc caataacctt accagcacgg ttcagggtgtt tactgactcg 3240
gagtaccagc tcccgtagt cctcggctcg gcgcacaaag gatgcctccc gccgttccca 3300
gcagacgtct tcatgggtgc acagtatgga tacctcacc tgaacaacgg gagtcaggca 3360
gtaggacgct cttcatttta ctgcctggag tactttcctt ctcagatgct gcgtaccgga 3420
aacaacttta ccttcagcta cacttttgag gacgttcctt tccacagcag ctacgctcac 3480
agccagagtc tggaccgtct catgaatcct ctcacagacc agtacctgta ttacttgagc 3540
agaacaaaac ctccaagtgg aaccaccacg cagtcaaggc ttcagttttc tcaggcccca 3600

gccagtgaca ttcgggacca gtctaggaac tggcttcctg gaccctgtta ccgccagcag 3660
cgagtatgaa agacatctgc ggataacaac aacagtgaat actcgtggac tggagctacc 3720
aagtaccacc tcaatggcag agactctctg gtgaatccgg ggcccggcat ggcaagccac 3780
aaggacgatg aagaaaagtt ttttcctcag agcgggggtc tcattcttgg gaagcaaggc 3840
tcagagaaaa caaatgtgaa cattgaaaag gtcattgatta cagacgaaga ggaaatccca 3900
acaaccaatc ccgtggctac ggagcagtat ggttctgtat ctaccaacct ccagagaggc 3960
aacagacaag cagctaccgc agatgtcaac acacaaggcg ttcttccagg catggtctgg 4020
caggacagag atgtgtacct tcagggggcc atctgggcaa agattccaca cacggacgga 4080
cattttcacc cctctcccct catgggtgga ttcggactta aacaccctcc tccacagatt 4140
ctcatcaaga acaccccggt acctgcgaat ccttcgacca ccttcagtgc ggcaaagttt 4200
gcttccttca tcacacagta ctccacggga cacggtcagc gtggagatcg agtgggagct 4260
gcagaacgaa aacagcaaac gctggaatcc cgaaattcag tacacttcca actacaacaa 4320
gtctgttaat cgtggacttt accgtggata ctaatggcgt gtattcagag cctcgcccca 4380
ttggcaccag atacctgact cgtaatctgt aattgcttgt taatcaataa accgtttaat 4440
tcgtttcagt tgaactttgg tctctgcgta ttctttctt atctagtctt catggctacg 4500
tagataagta gcatggcggg ttaatcatta actacaagga acccctagtg atggagttgg 4560
ccactccctc tctgcgcgct cgctcgctca ctgaggccgg gcgaccaaag gtgcggcgac 4620
gcccgggctt tgccccggcg gcctcagtga gcgagcgagc gcgcagagag ggagtgggca 4680
a 4681

<210> 19

<211> 4683

<212> DNA

<213> aav-6

<400> 19

ttggccactc cctctctgcg cgctcgctcg ctactgagg ccgggcgacc aaaggtcgcc 60

cgacgcccgg gctttgcccg ggcggcctca gtgagcgagc gagcgcgag agagggagtg 120
gccaactcca tcaactagggg ttcttgagg ggtggagtcg tgacgtgaat tacgtcatag 180
ggttagggag gtcctgtatt agaggtcacg tgagtgtttt gcgacatttt gcgacaccat 240
gtggtcacgc tgggtattta agcccagatg agcacgcagg gtctccattt tgaagcgga 300
ggtttgaacg cgcagcgcca tgccgggggt ttacgagatt gtgattaagg tccccagcga 360
ccttgacgag catctgcccg gcattttctga cagctttgtg aactgggtgg ccgagaagga 420
atgggagttg ccgccagatt ctgacatgga tctgaatctg attgagcagg caccctgac 480
cgtggccgag aagctgcagc gcgacttctt ggtccactgg cgccgcgtga gtaaggcccc 540
ggaggccctc ttctttgttc agttcgagaa gggcgagtcc tacttccacc tccatattct 600
ggtggagacc acgggggtca aatccatggt gctgggcccg ttcttgagtc agattagcga 660
caagctggtg cagaccatct accgcgggat cgagccgacc ctgcccact ggttcgcggt 720
gaccaagacg cgtaatggcg ccggaggggg gaacaagggt gtggacgagt gctacatccc 780
caactacctc ctgcccaga ctcagcccga gctgcagtgg gcgtggacta acatggagga 840
gtatataagc gcgtgtttaa acctggccga gcgcaaacgg ctcgtggcgc acgacctgac 900
ccacgtcagc cagaccaggg agcagaacaa ggagaatctg aaccccaatt ctgacgcgcc 960
tgtcatccgg tcaaaaacct ccgcacgcta catggagctg gtcgggtggc tgggtggaccg 1020
gggcatcacc tccgagaagc agtggatcca ggaggaccag gcctcgtaca tctccttcaa 1080
cgccgcctcc aactcgcggt ccagatcaa ggccgctctg gacaatgccg gcaagatcat 1140
ggcgtgacc aaatccgcgc ccgactacct ggtaggcccc gctccgcccg ccgacattaa 1200
aaccaaccgc atttaccgca tcttgagct gaacggctac gacctgcct acgccggctc 1260
cgtctttctc ggctgggccc agaaaagggt cggaacacgc aacaccatct ggctgtttgg 1320
gccggccacc acgggcaaga ccaacatcgc ggaagccatc gccacgccg tgcccttcta 1380
cggctgcgtc aactggacca atgagaactt tcccttcaac gattgcgtcg acaagatggt 1440
gatctggtgg gaggagggca agatgacggc caaggctcgt gagtccgcca aggccattct 1500

cggcggcagc aaggtgcgcg tggacaaaa gtgcaagtcg tccgcccaga tcgatccac 1560
ccccgtgatc gtcacctcca acaccaacat gtgcgccgtg attgacggga acagcaccac 1620
cttcgagcac cagcagccgt tgcaggaccg gatgttcaaa tttgaactca cccgccgtct 1680
ggagcatgac tttggcaagg tgacaaagca ggaagtcaaa gagttcttcc gctgggcgca 1740
ggatcacgtg accgaggtgg cgcattgagtt ctacgtcaga aagggaggag ccaacaacag 1800
acccgcccc gatgacgcgg ataaaagcga gcccaagcgg gcctgcccct cagtcgcgga 1860
tccatcgacg tcagacgcgg aaggagctcc ggtggacttt gccgacaggt accaaaaaca 1920
atgttctcgt cacgcgggca tgcttcagat gctgtttccc tgcaaaacat gcgagagaat 1980
gaatcagaat ttcaacattt gcttcacgca cgggaccaga gactgttcag aatgtttccc 2040
cggcgtgtca gaattctaac cggtcgtcag aaagaggacg tatcgaaac tctgtgccat 2100
tcatcatctg ctggggcggg ctcccagat tgcttgctcg gcctgcgatc tggtaacgt 2160
ggatctggat gactgtgttt ctgagcaata aatgacttaa accaggtatg gctgccgatg 2220
gttatcttcc agattggctc gaggacaacc tctctgaggg cattcggcag tggtagggact 2280
tgaaacctgg agccccgaaa cccaaagcca accagcaaaa gcaggacgac ggccggggtc 2340
tggtgcttcc tggctacaag tacctcggac ccttcaacgg actcgacaag ggggagcccc 2400
tcaacgcggc ggatgcagcg gccctcgagc acgacaaggc ctacgaccag cagctcaaag 2460
cgggtgacaa tccgtacctg cgggtataacc acgcccagcg cgagtttcag gagcgtctgc 2520
aagaagatac gtcttttggg ggcaacctcg ggcgagcagt cttccaggcc aagaagaggg 2580
ttctcgaacc ttttggctg gttgaggaag gtgctaagac ggctcctgga aagaaacgtc 2640
cggtagagca gtcgcccaa gagccagact cctcctcggg cattggcaag acaggccagc 2700
agcccgcata aaagagactc aattttggtc agactggcga ctacaggtca gtccccgacc 2760
cacaacctct cggagaacct ccagcaaccc ccgctgctgt gggacctact acaatggctt 2820
caggcgggtg cgcaccaatg gcagacaata acgaaggcgc cgacggagtg ggtaatgcct 2880
caggaaattg gcattgcgat tccacatggc tgggcgacag agtcatcacc accagcacc 2940

gaacatgggc cttgccacc tataacaacc acctctacaa gcaaattctcc agtgcttcaa 3000
cgggggccag caacgacaac cactacttcg gctacagcac cccctggggg tattttgatt 3060
tcaacagatt cactgccat ttctcaccac gtgactggca gcgactcatc aacaacaatt 3120
ggggattccg gccaagaga ctcaacttca agctcttcaa catccaagtc aaggagggtca 3180
cgacgaatga tggcgtcacg accatcgcta ataaccttac cagcacggtt caagtcttgt 3240
cggactcgga gtaccagttc ccgtacgtcc tcggctctgc gcaccagggc tgcctccctc 3300
cgttcccggc ggacgtgttc atgattccgc agtacggcta cctaacgctc aacaatggca 3360
gccaggcagt gggacgctca tcttttact gcctggaata tttcccatcg cagatgctga 3420
gaacgggcaa taactttacc ttcagctaca ccttcgagga cgtgcctttc cacagcagct 3480
acgcgcacag ccagagcctg gaccggctga tgaatcctct catcgaccag tacctgtatt 3540
acctgaacag aactcacaat cagtccggaa gtgccccaaa caaggacttg ctgtttagcc 3600
gtgggtctcc agctggcatg tctgttcagc caaaaaactg gctacctgga ccctgttacc 3660
ggcagcagcg cgttttctaaa aaaaaaacag acaacaacaa cagcaacttt acctggactg 3720
gtgcttcaaa atataacctt aatgggcgtg aatctataat caacctggc actgctatgg 3780
cctcacacaa agacgacaaa gacaagttct tccccatgag cgggtgtcatg atttttggaa 3840
aggagagcgc cggagcttca aacactgcat tggacaatgt catgatcaca gacgaagagg 3900
aatcaaaagc cactaaccct gtggccaccg aaagatttgg gactgtggca gtcaatctcc 3960
agagcagcag cacagaccct gcgaccggag atgtgcatgt tatgggagcc ttacctggaa 4020
tgggtgtggca agacagagac gtatactgc aggttctat ttgggccaaa attcctcaca 4080
cggatggaca ctttcaccg tctctctca tgggcggctt tggacttaag caccgcctc 4140
ctcagatcct catcaaaaac acgcctgttc ctgcgaatcc tccggcagag ttttcggcta 4200
caaagtttgc ttcattcatc acccagtatt ccacaggaca agtgagcgtg gagattgaat 4260
gggagctgca gaaagaaaac agcaaacgtt ggaatcccga agtgcagtat acatctaact 4320
atgcaaaatc tgccaacgtt gatttctctg tggacaacaa tggactttat actgagcctc 4380

gccccattgg caccggttac ctcaaccgct ccctgtaatt gtgtgttaat caataaaccg 4440
gttaattcgt gtcagttgaa ctttgggtct atgtccttat tatcttatct ggtcaccata 4500
gcaaccggtt acacattaac tgcttagttg cgcttcgga ataccctag tgatggagtt 4560
gccactccc tctatgcgcg ctgcctcgt cggtggggcc ggcagagcag agctctgccg 4620
tctgcggacc tttgggtccg aggccccacc gagcgagcga gcgcgcatag agggagtggc 4680
caa 4683

<210> 20

<211> 16

<212> DNA

<213> rep binding motif

<400> 20

gctcgtcgc tcgctg

16

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.